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Staphylococcal Pneumonitis in the Postoperative Patient*

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Because of its high mortality, staphylococcal pneumonitis commands the careful attention of all who practice medicine. In the postoperative patient this disease is a serious hazard which can turn a successful operation into a fatal catastrophe. On the basis of recent experience with 13 cases of postoperative staphylococcal pneumonitis, it is our aim to point out the need to recognize the disease early in its course and the necessity of treating it promptly and vigorously.

It is difficult to determine the incidence of staphylococcal pneumonitis and whether or not it is increasing in frequency. In Table 1 are recorded six chronologically arranged estimates of the incidence of the disease dating from 1919 to 1956. From this tabulation, no conclusions as to increase or decrease in frequency can be drawn. It is common knowledge, however, that the percentage of antibiotic resistant staphylococcal infections has increased in recent years. Pertinent to this paper is the occurrence of 13 cases of staphylococcal pneumonitis in postoperative patients in the years 1955 through 1958 among somewhat over 40,000 patients admitted to the Virginia Mason Hospital. Because of difficulties in diagnosis it is not unlikely that more cases actually occurred and were not recognized.

In Table 2 are recorded observations of percentage mortality due to staphylococcal pneumonitis by selected authors from 1919 to 1958. Despite antibiotic drugs, a high rate of mortality due to this disease persists.

In the light of the points discussed in the preceding paragraphs, this paper will be concerned with two major topics: first, a description of the clinical features of staphylococcal pneumonitis in postoperative patients, which allow its early recognition; second, comments on treatment will be presented based on the authors' experience with 13 postoperative patients afflicted with staphylococcal pneumonitis.

The Clinical Features of Staphylococcal Pneumonitis in Postoperative Patients

Classically, acute bacterial pneumonitis is readily recognizable by abrupt onset of general systemic symptoms (rigor, fever, and malaise);

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by respiratory manifestations of thoracic distress, cough, and dyspnea; by definite roentgenographic pulmonary densities; and by leukocytosis. Unfortunately, staphylococcal pneumonitis can be most difficult to recognize in the postoperative patient. As an example, the following case record is presented.

Case 1: Because of gross benign prostatic hypertrophy with obstructive urinary symptoms, a 63 year-old vigorous muscular carpenter underwent suprapubic prostatectomy. During the postoperative period, he manifested a low-grade fever, but ambulated and seemed to be progressing without difficulty toward adequate recovery. On the morning of the eighth postoperative day, he was found to have a fever of 104° F orally, a mild cough, and general malaise. Auscultation of the chest revealed minimal left basal inspiratory rales. At this time, urinary infection was suspected and tetracycline was given orally in a dose of ½ gm. every six hours. By the evening of the same day, he was markedly cyanotic, dyspneic, and in peripheral circulatory failure with blood pressure of 70/50 mm. of mercury. Tachypnea of 40 cycles per minute was noted and the minute volume of ventilation was estimated to be in excess of 40 liters per minute. Chloramphenicol was administered parenterally. In addition, intravenous fluids and a transfusion of whole blood were administered. Despite these measures the blood pressure remained low.

A vasopressor and hydrocortisone were administered by continuous intravenous drip. Detectable improvement did not occur. Finally, at 2:00 AM the next morning he suddenly expired. A graphic representation of this patient's course and therapy appears in Figure 1. In Figure 2 are reproduced his thoracic roentgenograms, one taken preoperatively, and one a few hours before death. The thoracic roentgenogram is striking in the lack of significant abnormalities.

At autopsy the tracheobronchial tree was found to contain large amounts of purulent material and bilateral widely disseminated pneumontis was discovered.

Although it is commonly held that staphylococcal pneumonitis tends to attack the very young, the aged, and persons rendered poor in de-

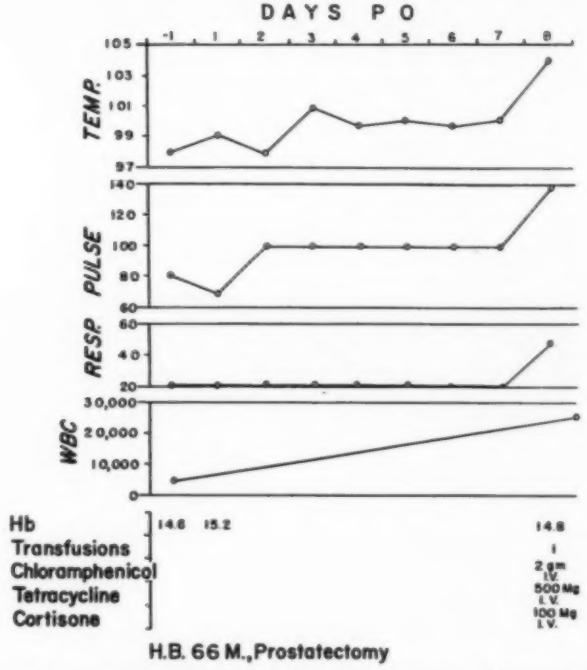

FIGURE 1: Graphic representation of Case 1, a 63 year old carpenter with *acute fulminating fatal staphylococcal pneumonitis,* abruptly striking the patient eight days after suprapubic prostatectomy. Death occurred in less than 24 hours.

TABLE 1—INCIDENCE OF STAPHYLOCOCCAL PNEUMONITIS

Year	Author	Total Pneumonias	Cases of Staph. Pneum.	Per cent Staph. Pneum.
1919	Chickering and Park[1]	800	13	1.6
1919	Chickering and Park[1]	1409 (influenza epidemic)	155	11.0
1927	Cole[2]	1383	19	1.4
1941	Gaspar[3]	144 (Autopsy)	38	26.4
1945	Michael[4]	72 (influenza epidemic)	5	6.9
1956	Hausman and Karlish[5]	122	18	14.8

fenses by concomitant diseases, it should be pointed out that untimely death occurred in the patient cited above. Furthermore, the individual concerned was a vigorous, muscular white man in whom an elective, stereotyped, otherwise uncomplicated operation was performed by a competent urologic surgeon. In addtion, physical and roentgenographic findings referable to the chest were quite meager. In fact, the diagnosis of staphylococcal pneumonitis during life was only suspected and not established until autopsy. It is noteworthy that this patient did not cough up sputum. Previously, Gresham and Gleeson-White[10] have pointed out the fact that staphylococcal pneumonitis often is difficult to recognize.

Among the 13 cases we have observed, a simple arbitrary classification has been evolved, based upon onset and course of the disease. Actually, our classification represents a modification of Finland's[6] classification of staphylococcal pneumonitis. The case record cited above (case 1) represents the acute fulminating fatal form of the disease, and occurred but once in our series. Our second category of disease is that of an acute critical form of postoperative staphylococcal pneumonitis, appearing eight times in the series of 13 cases. Of this group, two died. Characteristically, this form of illness is abrupt and violent in onset, and is terminated by death or by recovery within 20 days. It is exemplified in the following case record.

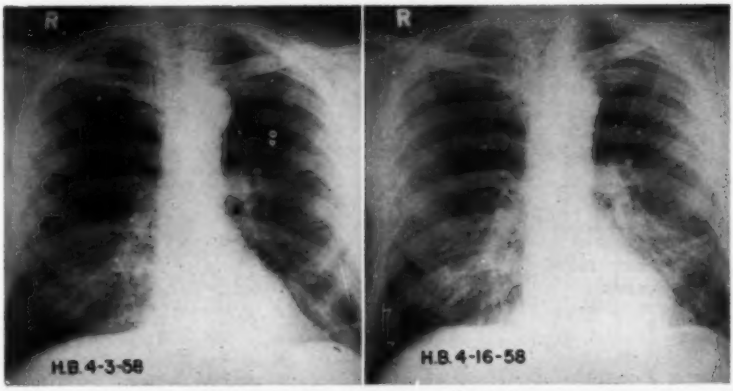

FIGURE 2: Roentgenograms of Case 1. That on the left was made preoperatively. The film on the right was obtained during the acute fatal illness on the eighth postoperative day.

TABLE 2—MORTALITY OF STAPHYLOCOCCAL PNEUMONITIS

Year	Author	Cases of Staph. Pneum.	Deaths	Per cent Mortality	Specific Drugs Available
1919	Chickering and Park[1]	13	10	76.1	None
1919	Chickering and Park[1]	155	153	98.6	None
1927	Cole[2]	19	13	68.4	None
1942	Finland, et al.[6]	66	21	31.8	Sulfonamides
1945	Michael[4]	5	2	40.0	Sulfonamides
1951	Gibson and Belcher[7]	10	0	0.0	Sulfonamides and Penicillin
1955	Muir, et al.[8]	9	5	55.5	Broad spectrum antibiotics
1956	Evans and Evans[9]	4	2	50.0	Broad spectrum antibiotics
1956	Hausmann and Karlish[5]	18	0	0.0	Broad spectrum antibiotics
1957	Gresham and Gleeson-White[10]	14	14	100.0	Broad spectrum antibiotics
1958	Fisher, et al.[11]	21	14	66.6	Broad spectrum antibiotics

Case 9: A 56 year-old retired fireman underwent a right chemopallidectomy for Parkinsonism. On the third day after the operation, he was given chloramphenicol. He seemed to do well until the fifth postoperative day, when he developed left hemiparesis. On the eighth postoperative day, he began to raise bloody sputum and to sweat profusely. He became disoriented, hyperpneic, and his temperature rose to

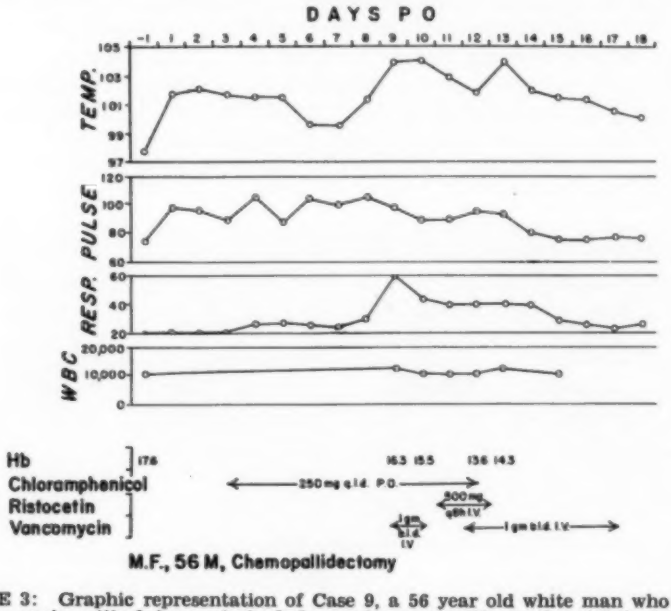

FIGURE 3: Graphic representation of Case 9, a 56 year old white man who developed an *acute critical form of staphylococcal pneumonitis* on the eighth day after chemopallidectomy. Abrupt onset of severe symptoms including respiratory frequency of as high as 60 cycles per minute is characteristic of this form of disease.

TABLE 3—CERTAIN FEATURES OF 13 CASES OF POSTOPERATIVE STAPHYLOCOCCAL PNEUMONITIS

Case No.	Age & Sex	Operation Performed	Post-op. day of onset	Rectal Temp. at onset °F	Degree of Dyspnea	Cyanosis	Character of sputum	Duration of illness in days	Outcome
1	66 M	Suprapubic Prostatectomy	8	104	severe	present	none	1	died
2	65 M	Thoracotomy	2	102	severe	present	copious, bloody and purulent	8	died
3	43 F	Mitral Commissurotomy	2	100	severe	present	copious, bloody and purulent	11	died
4	42 M	Thoracotomy	2	102	severe	present	copious, bloody and purulent	19	recovered
5	60 F	Thoracotomy	2	101	severe	present	copious, bloody and purulent	11	recovered
6	26 F	Tubal Ligation	1	98	severe	present	copious, bloody and purulent	15	recovered
7	38 M	Craniotomy	3	101	severe	present	copious, bloody and purulent	18	recovered
8	37 M	Bilat. Maxil. Antrotomy	2	101	severe	absent	copious, bloody and purulent	17	recovered
9	56 M	Chemo-pallidectomy	8	104	severe	present	copious, bloody and purulent	10	recovered
10	55 M	Renal Dialysis	3	99	severe	present	copious, bloody and purulent	35	died
11	63 M	Thoracotomy	3	100	severe	present	copious, bloody and purulent	20	died
12	58 M	Segmental Colectomy	2	103	slight	present	copious, purulent	21	recovered
13	52 M	Thoracoplasty	2	101	severe	present	copious, bloody and purulent	20	recovered

102° F. A respiratory frequency of 60 cycles per minute was recorded. In Figure 3, this patient's clinical course is presented graphically, and in Figure 4, his thoracic roentgenogram is reproduced. This demonstrated a left basal density. His sputum contained numerous gram-positive coccal forms. The diagnosis of staphylococcal pneumonitis was suspected and Vancomycin was administered intravenously. Additional means of treatment included inhaled nebulized bronchodilators, intermittent positive pressure breathing, and finally tracheostomy.

For five days after onset, he continued to be critically ill, but slowly improved. From the ninth to the eleventh postoperative day, he was given Ristocetin because of unavailability of Vancomycin. During this period he seemed to lose ground. After Vancomycin was resumed he improved.

On the 25th postoperative day, it was felt that in all likelihood he aspirated food because of his continued neural deficit. At this time, he seemed to develop pneumonitis with mixed bacterial flora. Vancomycin was increased from 1 to 2 gms. daily. Temperature again returned to normal in two days.

Following this episode, fever recurred for 10 days despite his apparent continued clinical improvement. At this time, it was felt that a drug reaction was likely, and Vancomycin was stopped. The fever abated, and he improved steadily thereafter. He was discharged to the care of his family physician on the 54th postoperative day.

A third class of postoperative staphylococcal pneumonitis is a protracted and exhausting form of the disease, insidious in onset, often becoming severe later in its course, but always characterized by slow response to therapy or by death in a period of 20 days or more. There were four patients with this form of the disease among our 13, of whom two died. An example is presented in the following report.

Case 12: A 58 year-old, somewhat obese, businessman, was subjected to segmental colectomy for diverticulitis. He was given penicillin and streptomycin postoperatively. On the first day after surgery, he raised rather thick sputum. On the third postoperative day, he suffered dehiscence of his operative wound. His sputum was clear at that time. The wound was closed secondarily. The following day, he became cyanotic, sweated considerably, and produced rather thick gray sputum. He was given chloramphenicol and on the third day after dehiscence of the wound, bronchoscopy was found necessary to relieve him of obstructing tracheobronchial secretions. Following this he improved steadily, and antibiotic therapy was discontinued on the ninth day following the secondary surgical procedure. Unfortunately, on the tenth day, he suffered increased respiratory distress. In Figure 5, his course and therapy are indicated graphically, and in Figure 6, thoracic roentgenograms are reproduced. The film taken on the tenth postoperative day demonstrated a nodular infiltrate in the right lung. With the discovery of this infiltrate, therapy with chloramphenicol was re-

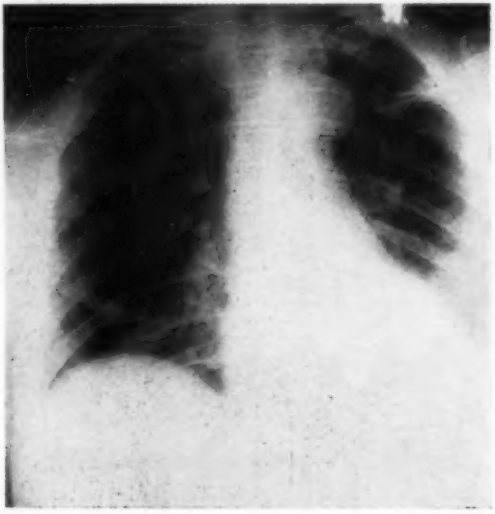

FIGURE 4: Thoracic roentgenogram of Case 9 taken on the eighth postoperative day showing a left basal density.

TABLE 4—SUMMARY OF TREATMENT OF 13 CASES OF POSTOPERATIVE STAPHYLOCOCCAL PNEUMONITIS

Case	Year of Infection	Sensitivity of Organism to Antibiotics								Antibiotics administered pior to or during onset	Antibiotics used in therapy of pneumonitis	Adrenal Cortico-steroids used	Outcome
		Pen	Str	Tet	Chl	Ery	Nov	Ole	Ris				
1	1958	H	H	H	H	H	H	—	—	none	Chl, Tet	+	died
2	1955	R	R	S	H	—	—	—	—	Pen	Str, Chl	+	died
3	1958	R	H	M	H	H	H	—	—	Pen	Chl, Ris	0	died
4	1955	R	R	R	H	—	—	—	—	Pen	Tet, Chl, Ery	0	survived
5*	1957	R R	MH R	R R	H R	H S	— H	H H	— —	Tet, Str	Chl, Ery, Nov	+	survived
6	1957	R	SM	R	MH	R	H	H	—	none	Chl, Tet, Ole, Nov	0	survived
7	1958	R	H	R	R	H	H	—	—	Chl	Van	0	survived
8	1958	R	H	R	R	H	H	H	H	Chl	Ris	0	survived
9	1958	R	H	R	R	H	H	—	—	Chl	Ris, Van	0	survived
10	1957	R	R	R	R	R	H	—	—	Chl	Tet, Ery, Nov, Ole	0	died
11	1957	R	R	R	H	S	H	—	—	Pen, Str	Nov, Ris, Van	+	died
12	1957	R	R	R	H	R	H	H	—	Pen, Str	Chl, Nov	0	survived
13	1958	R	M	R	R	R	R	M	H	Chl	Ris, Str	0	survived

*2 organisms isolated

H=highly sensitive
M=moderately sensitive
S=slightly sensitive
R=resistant
—=not tested

Pen=penicillin
Str=streptomycin
Tet=tetracycline
Chl=chloramphenicol
Ery=erythromycin
Nov=novobiocin
Ole=oleandomycin
Ris=ristocetin
Van=vancomycin

sumed, and two days later treatment with novobiocin was begun. Following this, he recovered rather rapidly and finally was discharged from the hospital on the 22nd postoperative day.

Follow-up examination disclosed complete clearing of the pulmonary lesions.

In order to portray the characteristics of the 13 cases of postoperative staphylococcal pneumonitis herein reported, Table 3 is presented. The clinical appearance of the onset of staphylococcal pneumonitis in the postoperative patient deserves amplification. A definite unexpected change for the worse in the patient's postoperative course usually attracts the clinician's attention. As pointed out previously, this change was abrupt in nine of the 13 patients herein reviewed (cases 1 through 9 of Table 3). In cases 10 through 13 (Table 3) the onset was insidious, and when fully developed, all but one (case 12) resembled the so-called acute fulminating (case 1) or acute critical (cases 2 through 9) forms of the disease. A striking feature was the fact that in only three of the 13 cases was the temperature over 102° F rectally at the time of recognized onset (cases 1, 9 and 12, of Table 3). Quite incongruous to the relatively low initial fever was the patient's degree of respiratory insufficiency. Typically, the patient was laboring for breath at respiratory frequency up to 60 cycles per minute. Airflow by crude clinical estimate was considered in excess of 40 liters per minute in most instances. Despite tachypnea and visibly uncomfortable hyperpnea, the patients were considered cyanotic (except case 8, Table 3). While the one patient with fatal fulminating disease (case 1) failed to raise sputum, all others had copious purulent sputum resembling frank pus. In 11 of the 13 cases, blood was apparent in the sputum raised. Diaphoresis, anxiety, and delirium were commonly, but not universally observed. Significant in the physical findings in the chest at onset was the lack of grossly abnormal

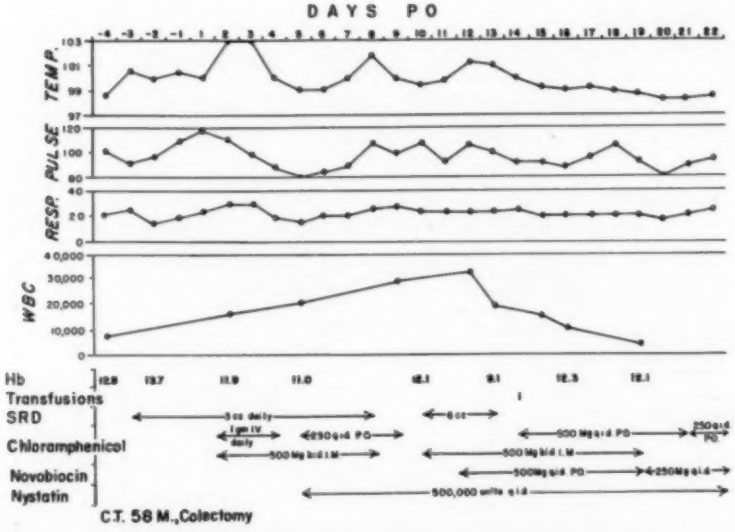

FIGURE 5: Graphic representation of Case 12. Here the postoperative days are referable to a secondary surgical procedure, i.e., closure of a dehiscence. This patient had *protracted exhausting form of postoperative staphylococcal pneumonitis* with rather insidious onset.

percussive and auscultatory signs. One exception, however, deserves special mention. In eight of the 13 patients, the expiratory phase of respiration was prolonged and accompanied by increased volume of auscultatory sounds, approaching wheezes in character. We have interpreted this finding as indicative of obstruction to airflow in small airways. Leukocytosis of 10,000 to 15,000 per cu. mm. was recorded at onset with a distinct rise as the disease progressed. Because of the common occurrence of leukocytosis, its presence in a postoperative patient should arouse one's suspicions of staphylococcal pneumonitis if other obvious causes for leukocytosis do not exist. Whereas cultures of fresh sputum revealed coagulase positive micrococci in large numbers (in all but case 1, where no sputum was obtained), gram-stained smears were considered valuable as early indicators of staphylococcal pneumonitis when large numbers of gram-positive coccal forms were revealed.

The Treatment of Postoperative Staphylococcal Pneumonitis

The treatment of staphylococcal pneumonitis will be discussed under the following headings: specific antibiotic therapy, measures directed at pulmonary insufficiency, and additional aids. In Table 4 is summarized the experience with the antibiotic sensitivity of the infecting organism, the antibiotics used prior to or during onset of the illness, and the specific antibiotics directed at the therapy of the recognized micrococcal infection. Interesting is the fact that case 1, terminating fatally, represented the only instance of a penicillin-sensitive staphylococcal infection. While this individual did not live long enough to establish the diagnosis of staphylococcal pneumonitis during life, it is interesting to speculate concerning his possible clinical course had he received a bactericidal antibiotic. Unfortunately, he was given only bacteriostatic antibiotics (tetracycline and chloramphenicol). An additional noteworthy point lies in the fact that all but two of the 13 patients were receiving an antibiotic at the time of onset of infection. Unfortunately, the infecting organisms were not sensitive to the antibiotics given. It is apparent, therefore, that the administration of common antibiotics to postoperative patients offers little protection against pneumonitis due to resistant staphylococci.

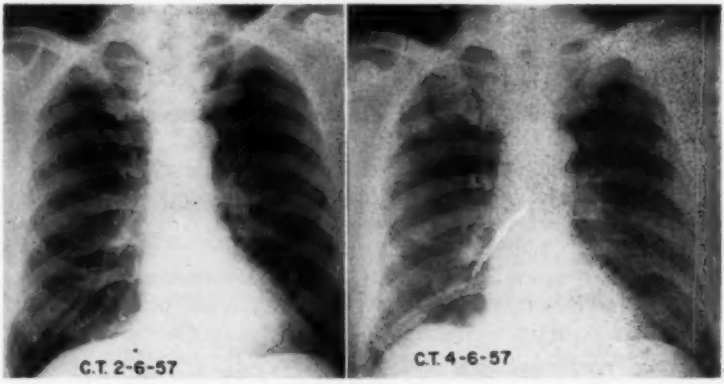

FIGURE 6: Case 12. Illustration on the left was taken preoperatively. The film on the right was taken 10 days after secondary closure of the original operative incision. It shows an almost nodular infiltrate in the upper lobe of the right lung.

Cases 2 and 3 died despite the administration of chloramphenicol, to which the infecting organisms were sensitive. Special mention pertinent to cause of death is indicated in cases 10 and 11, both fatal. In case 10, renal failure, following abdominal aortic surgery complicated the problem, and contributed to the patient's demise. In case 11, exsanguinating gastric hemorrhage was the precipitating factor in death, hence death could not be ascribed entirely to a poor response to Vancomycin. Also, in case 3, Ristocetin cannot be evaluated as failing, since it was not employed until three days before death occurred. Attention should be directed to cases 7, 8, 9 and 13, in which either Ristocetin or Vancomycin, or both, were employed. All of these patients had organisms resistant to chloramphenicol, as well as to penicillin. All were profoundly ill when Vancomycin or Ristocetin were administered, and all improved strikingly. In one patient, case 9, Vancomycin was employed initially, but because of inadequate supply of drug, Restocetin was substituted. During the two-day period of treatment with Ristocetin, the patient's fever increased, and his condition seemed to deteriorate a bit, only to improve again when treatment with Vancomycin was resumed.

Despite scanty evidence, we believe that prompt therapy with a bactericidal antibiotic by the intravenous route, preferably Vancomycin, is most likely to be successful in the treatment of staphylococcal pneumonitis in postoperative patients.

Since respiratory insufficiency in postoperative staphylococcal pneumonitis appears to be great, adequate therapy demands careful attention to measures designed to relieve the respiratory insufficiency. It has been our impression that a significant number of patients with staphylococcal pneumonitis have signs of obstructive ventilatory insufficiency. Hence we have used inhaled bronchodilators vigorously at frequent intervals up to every 30 minutes. Ordinarily we institute treatment at the bedside by hand-bulb nebulizer, such as DeVilbiss No. 40, containing a solution of isopropylarterenol. The generated mist is directed at the patient's nose and mouth, and eight to ten inhalations are allowed every 30 minutes. When the hand bulb nebulizer seems inadequate, an intermittent positive pressure breathing device with an attached nebulizer can be employed. Cyanosis, considered indicative of inadequate oxygen transport can be mitigated by continuous oxygen therapy via a humidifier and nasal catheter. When drowning secretions could not be controlled by adequate tussive force, supraglottal endotracheal aspiration, and bronchoscopic aspiration, tracheostomy was used in six of the patients (cases 5, 7, 8, 9, 10, 13).

Additional therapeutic aids used consisted of transfusions of whole blood and adrenal corticoids. Notoriously, staphylococcal infections produce either hemolysis or suppression of erythropoiesis. When anemia became apparent, replacement of blood was undertaken. There were four instances, three fatal, in which adrenal corticosteroids were used as adjuncts. What place this class of hormonal drugs plays is difficult to say from our experience. In case 5, the degree of obstruction to airflow seemed to warrant the use of prednisone for its anti-inflammatory action; the patient appeared to have benefitted from it, and she survived. No detectable aggravation of, or improvement in the underlying infection seemed to have occurred in this patient.

SUMMARY

Thirten adult postoperative patients afflicted with staphylococcal pneumonitis are reviewed. The surgical procedures included intracranial, facial, thoracic, cardiac, abdominal, urologic, and gynecologic operations. The onset of the disease occurred in the first three postoperative days in 10 of the 13 instances. When a postoperative patient manifests signs of severe resipratory insufficiency, incongruously low temperature, prolonged expiratory phase of respirations despite gross tachypnea and hyperpnea, purulent bloody sputum, and leukocytosis, staphylococcal pneumonitis must be suspected. This suspicion must be held despite singular lack of confirmatory roentgenographic changes in the lungs. A gram-stained smear of sputum demonstrating many gram positive coccal forms adds enough diagnostic evidence to initiate vigorous, aggressive therapy without delay. In view of the probability that the infecting staphylococcus will prove resistant to usual antibiotics, we advocate the prompt use of Vancomycin or Ristocetin intravenously. Because of gross respiratory insufficiency of obstructive type commonly present in postoperative patients with staphylococcal pneumonitis, inhaled nebulized bronchodilators, intermittent positive pressure breathing devices, and tracheostomy when indicated, have proved their value.

ACKNOWLEDGEMENT: The authors express deep gratitude to the Eli Lilly Company of Indianapolis, Indiana for the Vancomycin used in the patients herein described.

RESUMEN

En esta comunicación se revisan los casos de trece enfermos que han sufrido en el postoperatorio de neumonitis por estafilococos. Las operaciones que se les hicieron fueron intracraneanas, faciales, torácicas, cardiacas, urológicas y ginecológicas.

El principio de la enfermedad aconteciò en los primeros tres días postoperatorios en 10 de los trece casos.

Cuando en el postoperatorio los pacientes muestran insuficiencia respiratoria severa, hipotermia incongruente, expiración prolongada a pesar de existir gran taquipnea e hiperpnea, esputo purulento y sanguinolento y leucocitosis, debe sospecharse la neumonitis estafilocòccica. Esta sospecha debe mantenerse a pesar de la falta de cambios radiolègicos que la confirmen.

Un frotis con tinción al Gram del esputo que demuestre muchos ĉocos agrega evidencia diagnóstica para conducir a una actitud terapéutica vigorosa y agresiva.

En vista de la probabilidad de que se trate de esatfilococo que puede ser resistente a los antibióticos habituales, recomendamos el uso inmediato de la vancomicina o ristocetina por vía intravenosa.

A causa de la gran insuficiencia respiratoria del tipo obstructivo que es común en el postoperatorio de los enfermos con neumonitis estafilócóccica, son de valor probado las nebulizaciones con broncodilatadores, los aparatos con presión intermitente positiva y la traqueostomía cuando están indicados.

RESUMÉ

L'auteur fait le bilan de 13 malades ayant subi une opération chirurgicale, qui étaient atteints de pneumonie staphylococcique. Les interventions chirurgicales comprenaient des opérations intracraniennes, faciales, thoraciques, cardiaques, abdominales, urologiques et gynécologiques. L'apparition de la maladie eut lieu dans les trois premiers jours après l'intervention pour dix des treize cas.

Quand un malade qui a été opéré manifeste des signes d'insuffisance respiratoire grave, une température anormalement basse, une phase expiratoire prolongée, malgré une importante tachypnée et hyperpnée, une expectoration sanglante et purulente, une leucocytose, on doit soupçonner une pneumonie staphylococcique: cette suspicion doit être maintenue malgré l'absence de confirmation radiologique montrant des altérations radiologiques pulmonaires. Un frottis avec coloration de gram de l'expectoration montrant beaucoup de cocci-gram positifs ajoute une preuve diagnostique suffisante pour instaurer un traitement énergique, agressif sans délai. Parce qu'il est probable que le staphylocoque infectant se montrera résistant aux antibiotiques habituels, nous conseillons l'utilisation rapide de "vanomycine" ou de "ristocétine" intraveineuse. Etant donné l'insuffisance respiratoire importante de type obstructif communément présentée par ces opérés atteints de pneumonie staphylococcique, des aérosols de bronchodilatateurs, des cures de respiration en pression positive intermittente, et la trachéotomie si elle est indiquée, ont donné la preuve de leur efficacité.

ZUSAMMENFASSUNG

Bericht über 13 Erwachsene, die postoperativ an einer Staphylokokken-Pneumonie erkrankten. Die chirurgischen Maßnahmen betrafen intrakranielle und Gesichts-Operationen, thorakale, cardiale, abdominelle, urologische und gynäkologische Operationen. Der Krankheitsbeginn lag in den ersten drei postoperativen Tagen bei 10 von 13 Fällen.

Sobald Patienten in ihrer postoperativen Phase Zeichen von schwerer respiratorischer Insuffizienz erkennen lassen oder auch unangemessen niedrige Temperaturen, ein verlängertes Expirium in der Atmung trotz erheblicher Tachypnoe und Hyperpnoe oder blutig-eitriges Sputum und eine Leukocytose, muß man eine Staphylokokken-Pneumonie in Erwägung ziehen. An diesem Verdacht muß man auch dann festhalten, wenn bestätigende röntgenographische Veränderungen in den Lungen in seltenen Fällen fehlen. Eine Gram-gefärbtes Sputum-Präparat, in dem sich viele Gramm positive Kokkenformen nachweisen lassen, gibt einen ausreichenden diagnostischen Anhalt, um unvorzüglich eine intensive und aggressive Therapie einzuleiten. Im Hinblick auf die Wahrscheinlichkeit, daß die den Infekt bewirkenden Staphylokokken sich als gegenüber dem üblichen Antibiotizis resistent erweisen, empfehlen wir die alsbaldige Verwendung von Vanomycin oder Ristocetin iv.

Wegen der erheblichen respiratorischen Insuffizienz obstruktiver Art, wie sie gewöhnlich bei den Kranken in ihrer postoperativen Phase und bei der Staphylokokken-Pneumonie auftritt, haben inhalierte, vernebelte Bronchodilatatoren, Einrichtungen für intermittierende positive Druckatmung und gfls. auch eine Tracheotomie sich als eine wertvolle Hilfe erwiesen.

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Continued Observations on the Role of Steroid Therapy in Tuberculosis*

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Over the past four years, investigations at the Buffalo Veterans Administration Hospital relative to the role of adrenal steroids in the treatment of tuberculosis have progressed from preliminary trials in a few critically ill patients to expanding studies carried on with increasing confidence.

This therapy is based upon experimental evidence that cortisone will bring about a reduced reaction to tuberculoprotein in a tuberculin-sensitized animal. As a result, there is a diminution in exudate, a delay in tissue destruction, and the formation of fewer fibroblasts. At the same time, however, poorer localization of the infection and an increased multiplication of tubercle bacilli occurs.[1-5] A combination of adequate chemotherapy with the steroid should control these dangers, however, and still allow the beneficial anti-inflammatory effects.[6-7] In fact, chemotherapeutic agents are most effective when tubercle bacilli are actively multiplying and, theoretically, the decrease in exudate should permit the drugs to reach the organisms more readily.

Materials and Methods

Currently, 48 patients have been treated according to this combined regimen. All were men; 12 were Negroes. Ages ranged from 23 to 70 years, 20 of whom were between the ages of 35 and 45.

Of this group, 38 had far advanced pulmonary tuberculosis, one with concomitant meningitis; six had moderately advanced disease, and four had miliary tuberculosis associated with meningitis in two instances.

Early in the study, only those who had not responded to several months of combined chemotherapy were chosen for steroid treatment, thus allowing each patient to serve as his own control. As time progressed, we felt able to predict which patients would benefit from the combination and in such cases the steroid was started simultaneously with chemotherapy. Patients showing severe toxicity, high or persistent fever, unusual anemia, or marked malnutrition, as well as those with extensive acute exudative disease, miliary tuberculosis or tuberculous pneumonia were included in this category.

The first seven patients were treated with cortisone; since then prednisone has been used in 33 instances and methyl prednisone* in eight. To obtain the full benefit of the steroid, adequate initial dosage is essential. An initial dose of 60 mgm. of prednisone has been found most effective; this is reduced to 30 mgm. over a one week period and then continued at this level for three to four weeks. The drug is slowly and progressively decreased according to the schedule shown in Table 1, so

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*Kindly supplied by Dr. Andrew J. Moriarity of the Upjohn Laboratories, Kalamazoo, Michigan.

TABLE 1—CURRENT STEROID SCHEDULE

PREDNISONE — GIVEN FOR 2 - 2½ MONTHS	
60 mgm./day	3 days
45 mgm./day	3 days
30 mgm./day	3 - 4 weeks
20 mgm./day	2 - 3 weeks
15 mgm./day	1 week
10 mgm./day	1 week
5 mgm./day	1 week
ACTH GEL — 20 UNITS DAILY FOR 7 DAYS, STARTING DURING FINAL 3 DAYS OF PREDNISONE	

that total steroid administration extends over a two to two and one half months period. ACTH gel in a dose of 20 units daily is given for a week as the prednisone is discontinued. A similar routine using 80 per cent of the dose of prednisone has been followed in prescribing methyl prednisone. No dietary restrictions, supplemental potassium or routine antacids have been used with prednisone or methyl prednisolone.

Since the factor of adequate chemotherapeutic coverage is a vital one, we have attempted to insure this by limiting steroid therapy for the most part to original treatment cases. Thirty were treated with triple drug therapy; that is, a streptomycin-dihydrostreptomycin combination, isoniazid, and aminosalicylic acid. The remainder received INH and PAS or INH and streptomycin.

Results

Results with prednisone have continued to confirm those reported previously from our hospital.[8] Subjectively, the patients note a feeling of well-being and a pronounced increase in appetite. Objectively, they become afebrile within 12 to 24 hours, and remain so. Recurrence of fever should be considered of serious import, often indicating the onset of some complication.

Weight gain, representing true tissue gain and not fluid retention, begins after about a week on the combined program and continues progressively throughout the period of steroid therapy, averaging a total of 20 to 30 lb. The increase is somewhat greater and more rapid in those patients receiving the combined therapy early in their hospitalization.

Only 11 of the 48 patients had a hemoglobin of at least 13 gm. on admission and 23 had values below 11 gm. In the group receiving a period of preliminary drug therapy, no rise in hemoglobin occurred prior to adding steroids. However, immediately thereafter, an increase in hemoglobin was noted and all the patients had reached a hemoglobin level of at least 12 gm. at the end of a month on the combined regimen. The group who received immediate steroid therapy showed a similar prompt and impressive response. Such rapid rises to, and maintenance of, normal hemoglobin levels have not been seen in this type of patient on our service when treated with drugs alone. In patients in whom reticulocyte counts have been obtained, there has been a slight but consistent rise in reticulocytes, averaging 2 to 4 per cent, even in those patients with initial hemoglobin values of 12 to 13 gm. In several cases of reticulocyte response of 6 to 9 per cent has been noted. In all instances, the reticulocyte count has returned to below 1.5 per cent after about one month, even though the

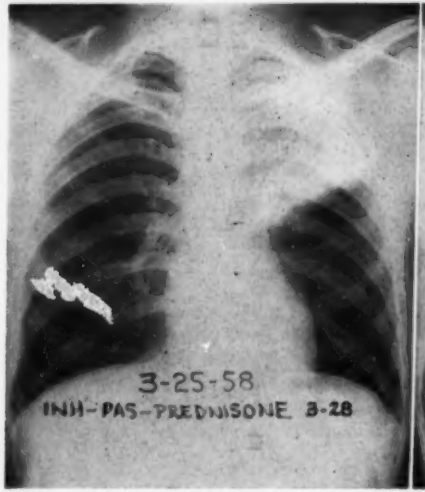

FIGURE 1: *Case 1—E.W.*—Admission chest x-ray film.

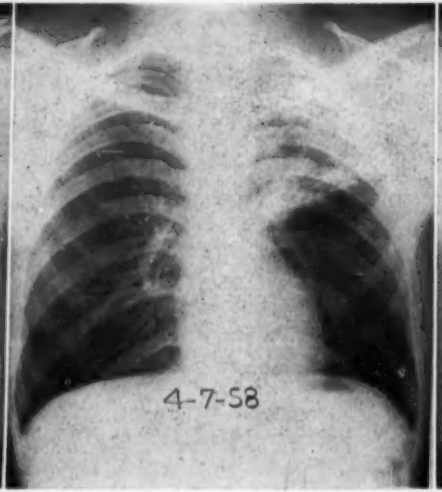

FIGURE 2: *Case 1*—After 10 days of INH, PAS, and prednisone.

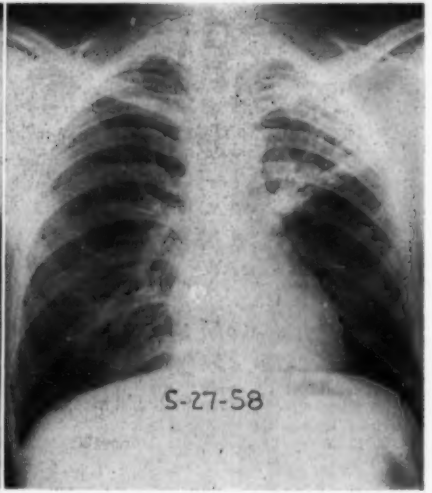

FIGURE 3: Case 1—After 2 months of combined therapy.

patient was still receiving steroid. While we are probably dealing primarily with the anemia of infection, the possibility of an associated hemolytic process which is inhibited by steroid therapy must be considered.

Bacteriologic results have shown no adverse influence of steroid therapy. Excluding those patients who have had less than three months of chemotherapy to date, only two failed to convert their sputum with drug therapy alone. Four others who have now received from three to seven months of chemotherapy are satisfactorily converting. The remaining patients, with one exception, all became negative on concentrate and culture prior to completing six months of treatment and this final case eventually converted also.

Radiologic improvement of a moderate degree is seen in most cases within the first two weeks after steroid is started and in acute disase the clearing is usually marked by the end of a month. Total improvement in some instances has appeared to be greater than might be expected with chemotherapy alone. No radiologic worsening has been seen in this series.

Complications have been few. One man developed a peptic ulcer and therapy was discontinued. An elderly man developed a spontaneous pneumothorax; any relationship to the steroid must remain speculative. Two cases of acute drug sensitivity were obscured by the prednisone, becoming apparent only when very low steroid dosage levels were reached. One receiving methyl prednisone showed an exacerbation of latent diabetes while under treatment and still required insulin after discontinuing the steroid. Only one instance of slight fluid retention occurred.

Although the number of cases treated with methyl prednisone is small, the effect on fever, hemoglobin response, and x-ray film clearing seems comparable to prednisone. There appears to be a lesser response with regard to appetite increase, weight gain, and improvement in morale, however.

Surgery

In this series of 48 patients, nine have been operated at our hospital. One pneumonectomy, three lobectomies, three segmental resections, and two definitive thoracoplasties have been performed. The time elapsed between discontinuation of the steroid therapy and surgery ranged from three to nine months. In none was additional steroid given at the time of surgery and all tolerated the anesthesia and operative procedures without difficulty.

The resected specimens have been carefully reviewed by the hospital consultant pathologist, Dr. Kornel Terplan. There appeared to be nothing grossly or histologically to distinguish this material from non-steroid treated tuberculous tissue; all the cellular elements usually seen were present and in some cases there was considerable fibrotic reaction. In all, acid-fast bacilli have been seen on smear, although cultures of several of these specimens were negative. Resistance studies on the positive cultures showed continued susceptibility to the three major drugs.

Follow-up Results

Twenty-one patients were first treated between January, 1954 and December, 1956. Current information is available on all but three. Seven of the 10 patients who interrupted their treatment are known to have received further therapy. Three of the group have died: one after only a few weeks of treatment for miliary disease, one from pulmonary tuberculosis and cor pulmonale, and the third of a myocardial infarction. Five have reached a closed negative or inactive status, three with the aid of surgery. The remaining eight are all "open negative" at the present time. Of those completing their original course of therapy, only one has had a transient bacteriologic relapse, on concentrate only, and no radiologic relapses has been seen. Six patients are still receiving chemotherapy. Three have emphysema which is severe enough to prevent them from working, but is not completely disabling.

The following demonstrates a typical response in tuberculous pneumonia and far advanced pulmonary disease.

H.W., a 38- year-old colored man, was admitted to the Buffalo Veterans Hospital on March 22, 1958, with tuberculous pneumonia involving the left upper lobe. On March 28, 1958, INH, PAS, and prednisone were begun simultaneously. His temperature immediately fell from 101° to 92°F; within two weeks he had gained 10 lb. and at the end of a month 20 pounds. His rapid x-ray film improvement is shown in Figures 1 to 3.

Discussion

In our experience, the addition of steroid therapy to chemotherapy can be safely recommended in the following types of tuberculosis: miliary disease, tuberculous meningitis, tuberculous pneumonia, and certain selected cases of severe far advanced pulmonary disease, particularly where a large exudative element is present or signs of toxicity are unusually pronounced. The anti-inflammatory effect of the adrenal steroids is non-specific. Presumably, in tuberculosis this effect is due largely to a reduction in the action of tuberculo-protein on sensitized cells.[1] There is additional evidence that malnourished patients with severe infections may show a decreased output of adrenal hormones and have relative adrenal insufficiency.[9] It must be emphasized that unless the associated tendency to poorer localization of the infection and bacteriologic multiplication is controlled by sufficient chemotherapy, the use of steroids can be hazardous. With adequate concomitant therapy, however, additional benefits of prompt defervescence, improved appetite and associated weight gain, rapid recovery from anemia, and the development of a sense of well-being can result in critically ill patients. In addition, there appears to be a more rapid and possibly more extensive radiologic improvement than would ordinarily be expected with chemotherapy alone.

Patients with less severe or more chronic forms of tuberculosis should not be expected to demonstrate such clear-cut gains. Although we are now expanding our study to included some less critically ill patients with modertaely advanced disease, it is too early to report definite conclusions. It would appear, however, that similar, though less dramatic, results are seen. Distinct and early x-ray film clearing occurs but it is difficult to determine whether this represents actual acceleration of the improvement expected from chemotherapy alone.

Patients who have received previous chemotherapy should receive steroids only after a thorough evaluation of possible drug resistance. As with all steroid therapy, patients with a history of peptic ulcer, heart disease or diabetes should be treated with caution. It should be remembered also that the use of steroids for non-tuberculous conditions in patients with either active or inactive tuberculosis requires similar judgment especially in reference to protective chemotherapy.

SUMMARY

1. Steroid therapy has been added to routine chemotherapy in 48 cases of active tuberculosis in an attempt to lower the mortality, shorten the period of toxicity, and improve the overall prognosis.

2. Results have shown a prompt reversal of toxicity, with the patients becoming afebrile, gaining weight and showing a striking rise in hemoglobin values. Sputum conversion has occurred in over 90 per cent of those treated six months or longer. Complications have been few.

3. In addition, x-ray film improvement appears to be accelerated and no adverse radiologic effects have been seen. Whether total improvement exceeds that to be expected without steroid is difficult to evaluate, but seems to occur in some cases.

4. Seven patients have undergone resectional surgery, and two have had thoracoplasties, without difficulty. Drug susceptibility has been retained. The resected specimens show no apparent differences from non-steroid treated cases.

5. This therapeutic combination is of definite value in patients with miliary tuberculosis, tuberculous meningitis, tuberculous pneumonia, and certain other selected cases of far advanced pulmonary disease. While its use in less severe forms cannot be routinely advocated, no harmful effect has as yet been noted in such cases.

RESUMEN

1. Con el objeto de disminuir la mortalidad, acortar el período tóxico de la enfermedad y mejorar en general el pronóstico de la tuberculosis, se ha ensayado agregar a la terapéutica habitual, el uso de los esteroides en 48 casos.

2. Los resultados han mostrado un inmediato retroceso de la toxicidad, haciendo a los enfermos afebriles, logrando que aumenten de peso y logrando un sorprendente aumento de la hemoglobina.

La conversión de los esputos ocurrió en más del 90 por ciento de los tratados por seis o más meses. Pocas han sido las complicaciones.

3. Además, la mejoría radiológica parece acelerarse y no hubo efectos radiológicos adversis observables. Es difícil estimar si la mejoría total excede a lo que era de esperarse sin los esteroides, pero parece que así es en algunos casos.

4. Siete enfermos se sometieron a resección y dos a toracoplastía sin dificultad alguna. La susceptibilidad a las drogas se conservó. Los especímenes de resección no muestran aparentes diferencias con los de enfermos no tratados con esteroides.

5. Esta terapéutica es claramente valiosa en los enfermos con tuberculosis miliar, meningitis tuberculosa, neumonía tuberculosa y otros casos escogidos de tuberculosis muy avanzada.

Si bien su uso en casos menos severos no es de recomendarse, no se ha encontrado daño alguno en tales casos.

RESUMÉ

1. Le traitement par les corticoïdes a été ajouté à la chimiothérapie habituelle dans 48 cas de tuberculose évolutive pour essayer d'abaisser la mortalité, diminuer la période de tovicité, et améliorer le pronostic.

2. Les résultats ont monté la sédation rapide de la toxicité, le malade devenant apyrétique, gagnant du poids et montrant une élévation frappante des taux d'hémoglobine. La négativation de l'expectoration est intervenue dans plus de 90% de ceux qui ont été traités pendant six mois et plus. Les complications ont été peu nombreuses.

3. En outre, l'amélioration radiologique semble être accélérée et on n'a pas vu d'évolutions radiologiques. Il est difficile d'évaluer si l'amélioration globale dépasse celle que l'on est en droit d'attendre sans l'utilisation des corticoïdes mais il semble qu'il en soit ainsi dans quelques cas.

4. Sept malades ont subi une chirurgie d'exérèse, et deux ont et des thoracoplasties, sans difficulté. La sensibilité au médicament a été maintenue. Les pièces de résection ne montrent aucune différence apparente par comparaison avec les cas non traités par les corticostéroïdes.

5. Cette association thérapeutique est de valeur précise chez les malades atteints de tuberculose miliare, de méningite tuberculeuse, de pneumonie tuberculeuse, et dans certains autres cas choisis d'affection pulmonaire avancée. Bien que son emploi dans des formes moins graves ne peut pas être conseillé d'une façon courante, jusqu'ici aucun effet nocif n'a encore été noté dans de tels cas.

ZUSAMMENFASSUNG

1. Sine Steroid-Therapie wurde der routinemässigen Chemotherapie hinzugefügt bei 48 Fällen von aktiver Tuberkulose mit dem Ziel der Herabsetzung der Mortalität, Verkürzung der Periode der Toxizität und Verbusserung der Prognose auf lange Sicht.

2. Die Resultate zeigten eine rasche Behebung der Toxizität; die Patienten entfieberten, nahmen an Gewicht zu und zeigten einen auffallenden Anstieg ihrer Haemoglobinwerte. Zur Sputum-Konversion kam es in über 90% bei einer Behandlung von 6 Monaten oder länger. Komplikationen waren gering.

3. Darüber hinaus scheint die röntgenologische Rückbildung beschleunigt zu werden, und ungünstige röntgenologische Wirkungen wurden nicht beobachtet. Ob die Besserung insgesamt gesehen diejenige übertrifft, die ohne Steroidbusatz zu erwarten war, ist schwer abzuschätzen, scheint aber in einigen Fällen vorzukommen.

4. Sieben Kranke wurden einer Resektionsbehandlung unterzogen, und zwei bekamen eine Thorakoplastik, sämtlich ohne Zwischenfälle. Arzneimittel-Empfänglichkeit blieb erhalten. Die Resektionspräparate zeigten keine deutlichen Abweichungen von den nicht mit Steroiden behandelten Fällen.

5. Diese therapeutische Kombination hat ihren definitiven Wert bei Kranken mit Miliartuberkulose, tuberkulöser Meningitis, tuberkulöser Pneumonie und bestimmten anderen ausgewählten Fällen weit fortgeschrittener Lungenkrankheit. Da ihre Anwendung bei weniger schweren Formen nicht routinemässig empfohlen werden kann, wurdenbis jetzt keine ungünstigen Wirkungen bei solchen Fällen bemerkt.

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Air Transport of Patients with Respiratory Disease*

PANEL DISCUSSION

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CLYDE MORSEY, Senior Engineer,
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Dr. Gordon: Long before the advent of aviation, man had mused in prose and poetry about the conquest of the upper atmosphere. Icarus of ancient Greece made the first though unsuccessful flight; others, in later generations, came to grief; a few were mildly successful. Theories and speculation mounted in the 19th century and balloon ascensions were commonplace, often hazardous. Then came the heavier-than-air flying machine — and the world-stirring flight of the Wright Brothers.

The modern air transport was born during the tensions of World Wars I and II, in the light of basic research and the magnificent contributions of engineering, physiology and clinical medicine. There are today, as a result, the jet engine, the pressurized cabin and operational instruments of the finest precision. Indeed, mechanical efficiency and passenger comfort have assumed a degree of ascendancy undreamed of a decade ago. These and other historical developments in air transport have been reviewed by Dr. A. H. Schwichtenberg, *(Clinical Cardiopulmonary Physiology,* Grune & Stratton, New York).

It is interesting that the pioneer aviator was chiefly concerned with his personal safety and protection of the aircraft; today's pilot is dedicated to the safety of passengers and vitally concerned about those who are being transported in other airplanes nearby. The term "safety," however, has assumed an even greater significance with the use of airplanes by patients with serious medical conditions, notably extreme cases of emphysema, asthmatic states, chronic bronchitis and the physiologic disturbances of the cardiopulmonary system associated with advancing age.

Medicine and surgery, as with aviation, are advancing at a breathless rate, especially definitive treatment as undertaken in specialized medical centers. Convalescence and rehabilitation often play an important role in recovery and patients not infrequently wish to enjoy the benefits of an equable climate to facilitate recovery. As a result, physicians are being called upon to advise on medical safety in air travel, the dangers of air sickness, the possibilities of an acute episode such as coronary insufficiency or some physiologic disturbance due to a sudden change in barometric pressure. Advice may be governed by knowledge of cardiopulmonary physiology and certain information on airplane construc-

*From the 25th Annual Meeting, American College of Chest Physicians, Atlantic City, June 3-7, 1959.

tion and operation. The present panel has been arranged for the considerations of "safety" in air travel. The participants have agreed that the exchange of views should be informal. The audience is invited to join in the discussions.

Mr. Clyde Morsey, Senior Engineer, Aircraft Engineering, American Airlines, will open the discussion on the mechanics of aircraft pressurization and operational measures provided for passenger safety.

Mr. Morsey: The cabin pressurization system is installed in airline aircraft solely to meet the needs of the human respiratory processes. The pressurization system makes it possible to maintain a low altitude in the cabin when the aircraft itself is at high flight altitudes.

For purposes of illustration, the cabin pressurization system may be considered in two parts. One of these is the source of pressure and the other is the control of the pressure. The source of pressure is usually provided by two or more compressors. These are driven either mechanically or pneumatically. That is, the compressor may be driven directly by a shaft or gear train from the engine, or, in the case of jet engines, by bleed air.

Where there are two compressors installed, either one is capable of maintaining nearly a full cabin differential pressure. On some jet aircraft there is in addition, an emergency source of pressure which consists of bleeding air directly from the engine compressor.

The cabin pressure control system regulates the cabin altitude, cabin rate of climb and cabin rate of descent. The term cabin altitude means the equivalent altitude inside the cabin produced by the pressurization system. Similarly the cabin rate of climb and descent are the rate of change of cabin altitude. Within the limits of the system capabilities these three items may be controlled somewhat independently of the aircraft operation. For example, if the aircraft were descending at a rate of 1000 feet per minute the cabin altitude might not necessarily be descending at all.

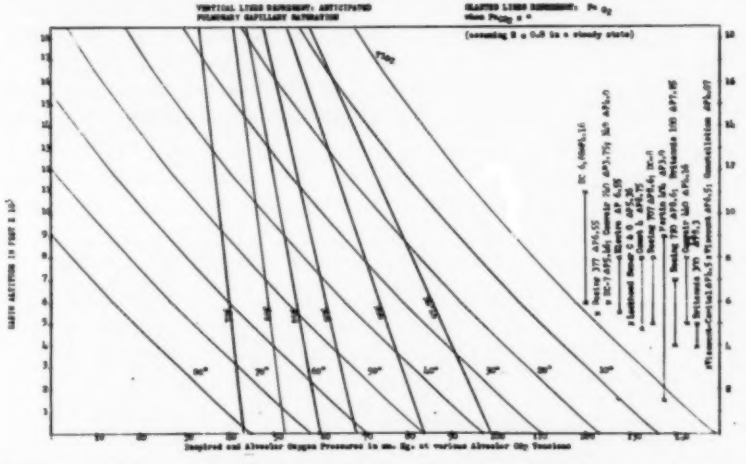

FIGURE 1: Pulmonary Capillary Saturation at Various Altitudes and Alveolar CO_2 Tensions.

As a means of illustrating how the cabin pressure is controlled you might consider the cabin as a large cylinder or tank. Compressors pump in air at one end and a valve controls the air flowing out the other end. Although the compressors are pushing in air at a fairly constant rate, the pressure and its rate of change may be controlled by adjusting the valve to bleed off the air as required.

The aircraft system operates in a similar manner. The control system automatically regulates the outflow valve to keep the cabin on a predetermined pressure schedule. The desired pressure schedule of cabin altitude, rate of climb, and descent, are set up by the crew in the cockpit. The control system then automatically maintains the schedule as set up. The pressurization system may also be controlled manually should there be a malfunction of the automatic system.

Speaking generally of the aircraft in the American Airlines fleet, on an average flight the cabin altitude should not exceed 8,000 feet, the cabin rate of climb 500 ft/minute and the cabin rate of descent 300 ft/minute. These figures are normal operating maximums and in most cases the actual figures would probably be somewhat better.

The aircraft structure is designed to keep to a minimum the possibility of cabin pressure loss. The fuselage construction is such that should certain parts fail, the load would be picked up by the surrounding structure. The cabin windows have double panes so that if one fails the other will take the load. On new aircraft a rip-stop type structural design will limit the propagation of a failure should one occur.

Dr. Gordon: Dr. Wilson, will you speak about the problem of transporting patients with respiratory disease? This seems appropriate after Mr. Morsey's comments on pressurization.

Dr. Wilson: The main problem to be considered is probably hypoxia. Doctor Gordon lives at 5800 feet; he is an adapted man. Where a person has been adapted, it is seldom that he will experience much more altitude in aircraft. However, a person living at sea level may have difficulty when suddenly required to adapt to an altitude as high as 8000 feet in

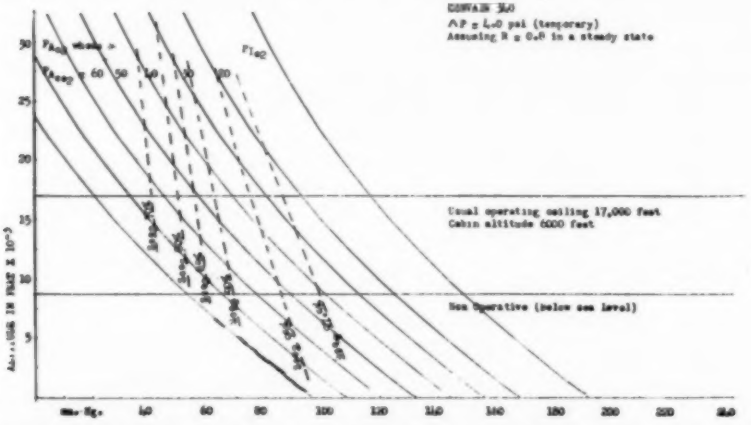

FIGURE 2: Pulmonary Capillary Saturation at Altitude and at Various Alveolar CO_2 Tensions. Example using specific aircraft operating at Δ P:4.0 psi.

certain instances. Figure 1, which is taken from a report to the Regents of the American College of Chest Physicians, shows the situation in a normal individual with regards to the transport of oxygen across the alveolar membrane. One can assume at altitudes of 5000 feet that acidosis becomes an important factor in relation to the saturation of blood in the pulmonary capillary. If this is so in the normal, it will be markedly worsened in the abnormal. Taking the specific plane in Figure 2, with a given diagram system one can predict the best flight conditions where the flight plan is known and pressurization follows the manufacturer's specifications.

The least considered factor and the one that I would like to stress most at this moment is the acidotic patient with emphysema, a disease syndrome that we are coming to consider more and more important today. One can see, using this kind of diagram, that acidotic patients, particularly when there is reason for their blood saturation to be low at sea level, may become seriously short of oxygen at altitude. In comparison of one aircraft and route with another, one starts to approach a flight plan for such a patient in which he will have the minimal altitude exposure and thus, presumably, will be transported with least deleterious effect to him. Thus we are concerned with patients who are potentially hypoxic either due to acidosis or some other reason. The physiologist must face problems of hypoxia in patients who normally live at a lower altitude than they travel.

Dr. Gordon: Doctor Stonehill, is it possible to decide accurately whether or not a patient should fly?

Col. Stonehill: In talking with numerous physicians around the country, it has become apparent that more and more ambulatory patients are asking them for advice as to whether they can travel by commercial airliners on an anticipated trip. Frequently, because of lack of experience in this field, the physician gives what he considers is a conservative answer and advises against flight. Unfortunately by not allowing the patient to utilize the speed and comforts of modern air liners, he may in actuality expose the patient to significantly more stress and exhaustion. Thus it becomes imperative that we acquaint ourselves with a method of clinically evaluating our chronic ambulatory cardiopulmonary patient with respect to air transportation.

There already has been considerable experience in moving patients by air. The aeromedical evacuation operations of the Military Air Transport Service has transported over 1.5 million patients. Two civilian air-

FIGURE 3: MANIFESTATIONS AT DIFFERENT ALTITUDES

Cabin Altitude	Condition
8,000 feet	Minimal Impairment
6,000 feet	Cyanosis + Emphysema + Restrictive Defect + Diffusion Defect
4,000 feet	Emphysema + indications of increased severity
	Severely affected cyanotic restrictive defect

liners also have moved thousands of patients. They are the Alaskan Run of Pan American Airways, and North Western Airlines, which carries patients to and from the Mayo Clinic.

All have reported that patients make good passengers. There are four problem areas, however:

a. Anxiety
b. Air sickness
c. Reduced pressure of oxygen
d. Reduced barometric pressure

Anxiety will increase the cardiopulmonary work load. The two greatest deterrents to anxiety are the reassurance given by the physician that the patient can safely make the trip by air, and the volume of passengers at air terminals going and coming in an unconcerned manner. Occasionally a mild sedative may be ordered prior to emplaning.

Airsickness results from a complex interplay of numerous stimuli. The use of anti-motion sickness medication, a light repast prior to boarding the aircraft, and prevention of anxiety will almost invariably control this most unpleasant symptom.

The reduction of barometric pressure to which a passenger is exposed is minimized by plane pressurization as explained by a previous panelist. Thus the reduction in the oxygen pressure inherent with altitude exposure is also minimized. An individual compensates for this slight reduction in oxygen pressure by mild hyperventilation and thereby maintains the oxyhemoglobin concentration. Thus the ability to hyperventilate with reasonable effectiveness and ease is the most important single physiologic consideration in pulmonary patients. Clinically, the patient must be at ease in a resting, sitting position and have a work tolerance for some greater degree of exercise. No patient with major cardiopulmonary disease should be exposed to a cabin altitude of greater than 8,000 feet. As the functional severity increases, this maximum exposure should be lower.

Dr. Gordon: It has been suggested that pressurized aircraft will soon become obsolete, and the sealed cabin may take its place. Dr. Wilson, would you care to express an opinion?

Dr. Wilson: My guess is that within 10 years pressurization will become totally impractical because we will be going far too high. In discussion with Dr. Buchanan Barbour, Medical Director of British European Airways, I learned that it was his opinion that within 10 years we will be able to go from New York or San Francisco to London in a sealed cabin, going as high as 30 miles. This could only be done with an artificial atmosphere.

FIGURE 4:—DATA PERTAINING TO THE "RESERVE" OF CARDIAC PATIENTS AT VARIOUS ALTITUDES:

Cabin Altitude	Condition
8,000 feet	Major cardiac disorders with adequate functional reserve at sea level
6,000 feet	Cardiac conditions where myocardial oxygenation is marginal

Dr. Gordon: How can we achieve this sealed environment? Mr. Morsey, perhaps your airline may be concerned with this at some future time.

Mr. Morsey: It is quite possible that we may some day use sealed cabins; however, the problems appear to be formidable. As the operating altitude continues to increase it will become more difficult to provide a practical means of compressing the air for the cabin. It would, however, appear that we could go substantially higher than we do today before the disadvantages of a ventilated cabin would offset the advantages.

In addition to the problem of compressing thin air there may also be the phenomenon of toxic gases.

At around 60 to 70,000 feet there appears to be an ozone concentration that becomes significant at times. This concentration apparently varies considerably with the time of year and geographic location. Although there may be other solutions, a sealed cabin should take care of this problem satisfactorily.

Dr. Gordon: Would you prefer sealed cabins for your patients, Col. Stonehill?

Col. Stonehill: Eventually, if we go very high, we will have to have sealed cabins.

Dr. Gordon: Are there other problems concerned with the sealed environment, Dr. Wilson?

Dr. Wilson: After all, in a sealed environment one must carry not only oxygen, but one must have something to absorb carbon dioxide. The very weight of such an absorbing material would make it unfeasible to have sealed cabins in today's airplanes, since the pay load would be nonexistent. One might have a situation where one has arranged to carry the patient but finds that there is insufficient pay load to allow the patient to be carried.

Dr. Gordon: Returning to our original problem about the safety of patient transport, are we justified in denying a patient air travel? Col. Stonehill, will you please discuss the evaluation of patients?

Col. Stonehill: I think it is entirely feasible to evaluate patients in clinical practice with simple means and to form a reasonable opinion as to how the patient may travel safely. In pulmonary disease we are interested in the functional capabilities of the patient, that he is stable (acute asthma, recent pneumonitis, and all these problems would be problems of unstable states). The three important situations in respiratory disease are those with serious obstructive defects as in emphysema, those with restriction of respiration as in pregnancy, pleural effusion, pleural fibrosis, etc., and lastly, where oxygen cannot pass into the pulmonary capillary. Patients with these defects, if minimal, should not go over 8,000 feet in our opinion. With increasing severity, we recommend lower altitude levels. In patients who are cyanosed, for example, 6,000 feet should be their ceiling. In cases of emphysema in the presence of acidosis of any degree the limit should be 4,000 feet. One must remember, however, that if oxygen is available on aircraft many patients will be able to fly safely. Referring to our report to the American College of Chest Physicians, we feel that we can divide patients according to the

severity of their syndrome. As for example, mild degrees without clinical signs 8,000 foot ceilings would be satisfactory; with cyanosis a 6,000 foot ceiling is required; and in acidosis 4,000 feet should be the limit. In very severe cases, careful consideration must be made before airplane travel is permitted. Cor pulmonale, incidentally, would fall into the category of a second factor. This is emphasized in Figure 3.

Dr. Gordon: Dr. Wilson, are there further aspects in selecting patients?

Dr. Wilson: We are up against a great difficulty which has nothing to do with medicine itself. It is the fact that a private, commercial airline wishes to avoid death and illness on planes because it is distressing to other passengers and because it may completely alter flight plan with consequent delays which are expensive. In air transport today we have an extremely low death rate. This is because most patients with a serious physical disturbance are told not to fly. If we take people on aircraft with known heart or lung disease, the death rate is bound to increase. However, we are not taking into account the patient who does board an airplane, despite illness, or the patient who is relatively unconscious of the fact that he should not fly. By pooling information between physician and airline, we can plan safe ways for patients to travel. For example, a patient who wants to go from San Francisco back to Italy and does not wish to take the boat should fly across the continent rather than take the train or the bus. It is obviously more comfortable, less tiresome, and the altitude exposure is less (Figure 4).

Dr. Gordon: Is smoking a disturbing influence in air travel?

Dr. Wilson: There are patients who we suggest should not smoke. It is equally true that they should not smoke on an airplane, or even more true. However, the ardent smoker is unlikely to stop smoking. One must remember that a cigarette in the hands of a frightened or anxious person may have considerable usefulness in soothing him. What do you think, Dr. Stonehill?

Col. Stonehill: I don't think basically that smoking on aircraft is any different than smoking on the ground, although it will raise the physiologic altitude level in the experimental animal. That is to say, the animal responds as if he is 2,000 or 3,000 feet higher than the altitude to which he is exposed. Therefore, it is probably desirable for the patient who is reassured about flying that he should not smoke in flight. Yet the loss by telling him that he should not smoke may be greater than the gain of his not smoking.

Dr. Gordon: What about the metabolic problems such as may occur in diabetes? For example, if a well-controlled diabetic becomes air sick and vomits profusely he may become quite ill. With dehydration the manifestations may become serious. Will you discuss this, Dr. Wilson?

Dr. Wilson: Of course, it is possible that a diabetic in this situation might pass into coma. Here one returns to the old problem of how to deal with air sickness before it occurs. Vomitus bags are not the answer.

Col. Stonehill: I'm glad to see those bags!! Of course the important thing, too, is not so much coma as the possibility that the patient will develop hypoglycemia.

Dr. Irving Mack (from the audience): What are the approximate figures for average cabin altitudes in long flights of commercial planes? What does the panel think about sickle cell anemia, severe scoliosis, etc.? Also I would like to comment that anxiety in the cardiac patient often occurs while he is still on the ground, and his symptoms may appear before take-off.

Dr. Wilson: In commercial aircraft at present, it is uncommon to go above 10,000 feet unless a catastrophe such as a window blowout should occur. The average jet plane has a ceiling of 45,000 feet, at which point the cabin altitude is nearly at 8,000 feet. However, there are planes which do not go so high as they are designed. Many jet flights across the continent actually occur at 30,000 to 35,000 feet only, and such flights have a cabin altitude below 5,000 feet. Also, there are planes designed with high pressurization which do not fly at considerable altitudes such as the Boeing 377 and the Viscount. Surely the important thing is to get from the airlines the approximate flight pattern or to provide important information about the patient so the pilot can plan accordingly and route the plane so that the patient does not go above a certain altitude.

Dr. Gordon: Will you amplify these considerations, Col. Stonehill?

Col. Stonehill: There is no rule that passengers cannot be exposed to altitudes over 10,000 feet. It is merely that above 10,000 feet, additional oxygen must be available. Since this is expensive and reduces the pay load, generally, unpressurized aircraft do not go above this limit. On principle, short flights are generally very safe, particularly with the more modern equipment. "Hedgehopping" is perhaps a good thing to consider with cardio-respiratory difficulties. With regard to sickle-cell anemia, one must remember that 9 per cent of the Negro population has a sickling problem which may give rise to intravascular thrombosis and to vascular hemolysis. In general, it is suggested that suspect patients should not go over 6,000 feet altitude and should have oxygen in flight.

Dr. Gordon: Do you think the ability to climb the stairs into the airplanes without respiratory embarrassment is a test of the patient's physiologic capacity, Col. Stonehill?

Col. Stonehill: This is certainly something to consider as to whether or not a patient can fly.

Dr. Gordon: Accordingly, if a patient is breathless on climbing the stairs his condition may be considered somewhat unsatisfactory for flying.

Dr. Howard Andersen (from the audience): What about the development of a spontaneous pneumothorax during flight?

Dr. Wilson: This seems of greatest importance when it pre-exists as a therapeutic procedure or a pneumoperitoneum, and similarly in cases of distended abdomen due to gas. The gas will expand, causing an elevation of the diaphragm, tending to reduce lung volume.

Col. Stonehill: I would like to ask Dr. Morsey what happens when we lose pressurization.

Mr. Morsey: As was mentioned earlier, the system and aircraft are designed to keep cabin pressure losses at a minimum. Should a loss of

pressure occur, however, there is an oxygen system available. On aircraft certified to operate above 25,000 feet the oxygen system is quite automatic. If the cabin altitude should go higher than 14,000 feet the system turns on automatically and masks automatically drop out for each passenger. To assist in rapid application of the mask it is circular in shape. With this shape the mask does not require special orientation when placing it on the face.

Dr. Hollis Johnson (from the audience): Is there a problem of carbon dioxide accumulation on airplanes?

Dr. Wilson: No, in actual fact there is almost complete renewal of the atmosphere in an airplane every minute or two. Actually, the ventilation is a good deal better in an airplane than it is in a room at home.

Dr. Gordon: Will you comment on this very interesting feature, Mr. Morsey?

Mr. Morsey: On a typical 70 passenger airplane, air is being pumped in at the rate of approximately 110 lbs. per minute. This provides a complete change of air in the cabin every few minutes so that it flushes out the carbon dioxide.

Dr. Johnson: In a sealed capsule, however, there is going to be a CO_2 problem.

Dr. Wilson: The answer would concern the efficiency of fuels and rocket engines, which we cannot go into now. Although liquid oxygen may solve the oxygen need in a sealed cabin, we certainly have not discovered how to cope with CO_2 accumulation.

Dr. Kunstler (from the audience): What preventive regimen do you suggest for motion sickness?

Col. Stonehill: Firstly, try to remove the patient's doubts about comfort and safety. Secondly, an antimotion sickness pill such as Dramamine or Bonamine should be taken about one half hour before take-off. Lastly, an immobilization of the head and leaning back with the eyes closed, are of considerable assistance. Incidentally, I would like to comment that this is of particular importance on economy flights which often have the additional problem of night travel.

Dr. Gordon: What about air embolism with sudden change of altitude in the plane, Dr. Wilson?

Dr. Wilson: It is rare. However, it is perhaps something we should keep in mind.

Dr. Gordon: What about alcohol on planes, Col. Stonehill?

Col. Stonehill: This is a very controversial question. However, again we know that it does increase the physiologic altitude.

Dr. Wilson: Leaving out the question of moral issues of alcohol, one has on the one hand the reassurance and feeling of well being from a small cocktail; on the other hand, there is the problem of the patient who has overindulged before flight. It would seem that alcohol in moderation may be actually a useful medication to relieve anxiety, reduce air sickness and produce a feeling of familiarity and casualness.

SUMMARY

Dr. Gordon: Today's discussion of air transport for patients has emphasized the importance of collaboration in developing the various factors of safety and comfort. Indeed, the basic considerations have not occurred by chance but rather through the important avenues of pulmonary physiology, engineering and clinical medicine. As a result, air sickness, oxygen-lack, anxiety states and fatigue are rare. The pressurized cabin with stabilization and precision operation are notable contributions. There remains, however, the need for the thoughtful evaluation of cases with actual or potential coronary insufficiency, hypertension and cor pulmonale in emphysema, especially in aging persons. Reference was made to the report on aviation medicine of the American College of Chest Physicians concerning the selection of borderline cases.

Many thanks to the panelists for their important communications; and to the audience—thank you for coming.

RESUMEN

La consideración del transporte aéro para enfermos, ha hecho destacar la importancia de la colaboración para crear los diversos factores de seguridad y de comodidad. De hecho las consideraciones fundamentales no han ocurrido por azar, sino más bien a través de los amplios caminos de la fisiologóa pulmonar, de la ingeniería y de la medicina clínica.

Como resultado, el marco, la falta de oxígeno, los estados de ansiedad, son raros. La cabina de presión compensada, la estabilización con operaciones precisas son una contribución notable. Sin embargo, queda la necesidad de una cuidadosa evaluación de los casos con insuficiencia coronaria o que potencialmente pueden presentarla, los de hipertensión y cor pulmonale en enfisema especialmente en las personas de edad avanzada.

Se hace referencia al informe sobre medicina de aviación del American College of Chest Physicians con respecto a la selección de los casos límites.

RESUMÉ

La discussion actuelle sur le transport aérien des malades a mis l'accènt sur l'importance de la collaboration pour développer les divers facteurs de sauvegarde et de confort. Les considérations fondamentales ne sont pas apparues au hasard, mais plutôt à travers les voies importantes de la physiologie pulmonaire, la mécanique et la clinique médicale. Il en résulte que le mal de l'air, l'anoxie, les étafs d'anxiété et la fatigue sont rares. La cabine pressurisée, la stabilisation avec des appareils de precision en sont une contribution notable. Reste cependant la nécessité d'une estimation des cas atteints d'insuffisance coronarienne actuelle ou virtuelle, d'hypertension et de coeur pulmonaire avec emphysème, surtout chez les personnes âgées. L'auteur s'est référé au rapport sur la médecine de l'air de l'American College of Chest Physicians, concernant la sélection des cas limites.

ZUSAMMENFASSUNG

Die gegenwärtige Diskussion der Beförderung von Kranken auf dem Luftwege hat die Wichtigkeit einer Zusammenarbeit herausgestellt hinsichtlich der Entwicklung der verschiedenen Momente der Sicherheit und der Bequemlichkeit. In der Tat sind die grundlegenden Erwägungen nicht rein zufällig zustande gekommen, sondern weit mehr dank der wichtigen Eröffnungen der Lungenphysiologie, der Technik und der klinischen Medizin. Infolgedessen wurden die Luftkrankheit, der Sauerstoffmangel, Angstzustände und Ermüdbarkeit selten. Die Druckkabine, die Stabilisierung mit genauer Wirksamkeit sind ein bemerkenswerter Beitrag. Es bleibt jedoch die Notwendigkeit für eine sorgsame Betreuung der Fälle von beztehender oder möglicher Coronarinsuffizienz, Hypertension und cor pulmonale beim Emphysem, besonders bei älteren Personen. Es wurden Hinweise gegeben zu dem Bericht über Luftfahrtmedizin des American College of Chest Physicians, die die Auswahl von Grenzfällen betrifft.

Clinical Experiences With Intravenous Colchicine in Inoperable Bronchogenic Carcinoma

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Introduction

The markedly increasing incidence of cancer of the lung observed during the past two decades has emphasized the urgent need for its early diagnosis.[1] It is probably a fair estimate that by and large approximately 60 per cent or more of patients with pulmonary malignancy are inoperable on admission.[2,3] Of the remainder that are explored, about one-half have a non-resectable lesion; and of the group that is resected, the five year survival rate ranges approximately between 5 to 25 per cent.[1,2,4-8]

It is obvious, therefore, that at present palliative measures are the fate for most patients with bronchogenic carcinoma. Especially intriguing and potentially fruitful is the area of current research for new chemotherapeutic and anti-mitotic agents.

Purpose

Colchicine, used primarily in clinical medicine for the treatment of gout, has long been known to have cytotoxic, anti-mitotic and anti-tumor properties on the basis of *in vitro* and *in vivo* experimental studies.[9-21] However, published experiences relative to its application in human cancer have been few.[12,22-27,31] Recent access to a new intravenous preparation of Colchicine (1.0 mg. per 2 cc. ampoule) prompted our clinical investigation into the possible efficacy and toxicity of the drug in inoperable cases of bronchogenic carcinoma.

Method

Twenty patients with inoperable pulmonary cancer were divided into the following categories:

Group I: These patients were treated with colchicine intravenously without associated supplementation of x-ray therapy. The alkaloid was given in the following dosage according to body weight; (a) 2.0 mg. (per injection) for patients below 130 lbs.; (b) 4.0 mg. for patients 130-150 lbs.; (c) 8.0 mg. for patients above 150 lbs. This group was subdivided into two classes according to the frequency of administration of colchicine:

(A) Five patients received the above dosage weekly for three consecutive injections. This was followed by a three week rest period; colchicine therapy was then resumed as mentioned above for three more weekly injections. The total amount of colchicine given per patient ranged from a minimum of 12 mg. to a maximum of 30 mg. with an average of 18 mg.

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This investigation was supported by a grant from Eli Lilly and Company. The colchicine was also supplied by the same company.

TABLE 1—RESPONSE TO THERAPY
COMPOSITE OF GROUP 1A and 1B (COLCHICINE TREATED)
TOTAL — 10 CASES†

	Number	Response** E	M	S	N
Chest Pain	8	0	1	3	4
Productive Cough	8	0	0	4	4
Hemoptysis	5	0	0	1	4
Weight Loss	7	0	1	1	5
Wheezing	3	0	0	0	3
Dyspnoea	2	0	0	0	2
Feeling of "Well Being"	4	0	3	1	0
Superficial Nodes	4	0	0	0	4
Osteoarthropathy	3	0	0	0	3
Chest X-ray Film Findings	9*	0	1	0	8

*Chest X-ray Film of patient who had pneumonectomy prior to institution of this regimen but later had clinical evidence of mediastinal involvement — not included in this evaluation.

**E=excellent; M=moderate; S=slight; N= no response

Excellent: Significant improvement maintained for at least 3 months.
Moderate: Significant improvement maintained between 1-3 months.
Slight: Significant improvement maintained for less than 1 month or minimal improvement over a longer period of time.

†Evaluation made as of September 1, 1958.

(B) Five patients received colchicine intravenously in the same dosage as above, three times weekly for four weeks, then twice weekly for four weeks, followed by one injection weekly for four doses unless intolerance developed or death intervened. The total amount of colchicine administered per patient ranged from 18 to 48 mg. with an average of 32.8 mg. The average amount per patient for the total group of 10 cases was 25.4 mg.

Group II: A total of ten patients received both colchicine and conventional x-ray therapy. The latter was administered in the dosage of 2000-3000 roentgens in air over each port; six had three ports and four had two. These cases were also divided into two classes:

(A) Eight patients received colchicine (as per body weight cited above) at two week intervals for three doses. After a rest period of three

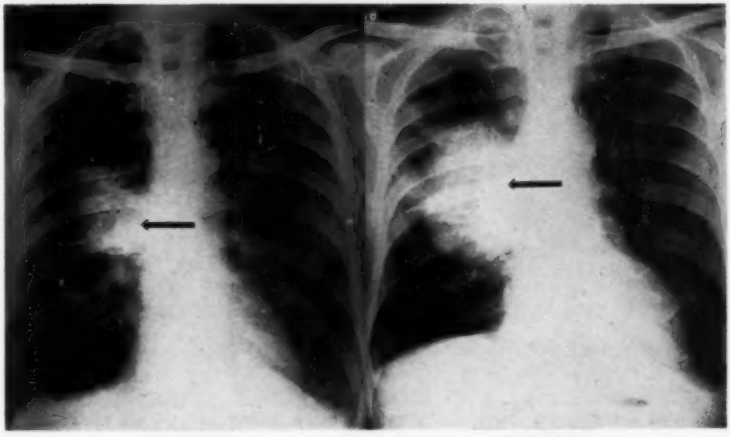

FIGURE 1

FIGURE 2

TABLE 2—RESPONSE TO THERAPY
COLCHICINE — X-RAY TREATMENT GROUP2 — 10 CASES†

	Number	Response E	M	S	N
Chest Pain	7	0	4	3	0
Productive Cough	10	0	7	3	0
Hemoptysis	5	0	3	2	0
Weight Loss	6	1	4	0	1
Wheezing	1	0	1	0	0
Dyspnoea	1	0	1	0	0
Feeling of "well being"	4	1	1	2	0
Superficial Nodes	3	0	0	0	3
Osteoarthropathy	2	0	0	0	2
Chest X-ray Film Findings	9*	2	2	0	5

*Chest X-ray Film of patient who had lobectomy prior to institution of this regimen not included in this evaluation (See text).
†Evaluation made as of September 1, 1958.

weeks, irradiation was instituted. After completion of x-ray therapy, another three week rest period ensued and then colchicine intravenously was resumed in the same manner. The average dose was 19.5 mg. per patient.

(B) Two patients received colchicine once weekly for three doses concurrently with the initiation of irradiation. The average amount of colchicine given was 12 mg.

TABLE 3—LENGTH OF SURVIVAL

	Group 1 (Colchicine) 1A	1B	Composite Groups 1A and 1B	Group 2 Colchicine and X-ray
Cases	5	5	10	10
Age (average)	63.4	59.8	61.6	59.2
Time interval (mos.) from onset of symptoms/signs to onset of palliative R_x	7.8*	10	9	8.8
Dead	4 (80 per cent)	5 (100 per cent)	9 (90 per cent)	8 (80 per cent)
Age (average)	61.2	59.8	60.4	61
Time interval (mos.) from onset of symptoms/signs to onset of palliative R_x	7.8	10	9	9
From onset of R_x to death (mos.)	5.5	5.8	5.7	6.4
From onset of symptoms/signs to death (mos.)	13.3	15.8	14.7	15.4
Living	1 (20 per cent)	0 per cent)	1 (10 per cent)	2 (20 per cent)
Age	72			48 and 56 years
Time interval (mos.) from onset of symptoms/signs to palliative R_x	?*			3 and 13 months
From onset of R_x to Sept. 1958 (mos.)	15		15	15 and 20 months
From onset of symptoms/signs to Sept. 1958 (mos.)	?*			18 and 33 months

*Patient was transferred from the Mental Disease Hospital and an accurate determination of duration of symptomatology could not be made.

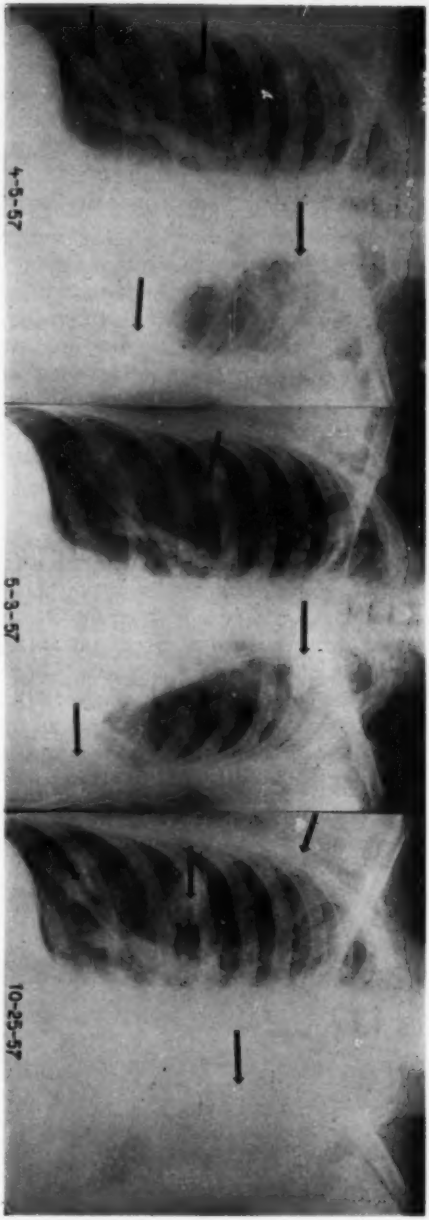

FIGURE 3

FIGURE 4

FIGURE 5

The average dose for the entire group of ten patients was 18 mg. with a minimum and maximum range from 12 to 48 mg. Cortisone was administered empirically in these patients in an attempt to minimize radiation pneumonitis, pleuritis and fibrosis. The steroid was given in divided doses, totalling 100 mg. daily during the use of x-ray therapy and for one month after its completion. Concomitantly, the patient received a low salt diet, 3 grams of potassium chloride daily and 300,000 units of penicillin daily (or 2.0 grams daily of Gantrisin if followed in the out-patient department after discharge). When cortisone was terminated, two doses of ACTH-gel (40 units at 12 hour intervals) were given. To lessen the possibility of osteoporosis and for its protein anabolic effect, depotestosterone (100 mg.) was administered intramuscularly every two weeks.

All of the patients received the colchicine before breakfast and 50 mg. of chlorpromazine was given intramuscularly prior to each injection. Penicillin or a broad spectrum antibiotic was administered during hospitalization to all patients soon after admission. Supportive therapy, including blood transfusions, was employed as indicated. Frequent chest x-ray films, blood counts (including platelet counts) as well as other pertinent procedures, supplemented the clinical notations in the follow-up observation of these patients.

Results

Before commenting on the results of treatment, a few general remarks about the two groups of patients are merited. All of the 20 patients were white men and the average age was similar (61.6 and 59.2, respectively). The two groups were also comparable in that the duration of illness from onset of symptoms to institution of palliative therapy was 6.7 months and 8.6 months, respectively. All 20 patients had a cigarette smoking history, with 16 classified as moderate to heavy smokers.* Cytological studies of the sputum and/or bronchial secretions were positive for cancer cells in 18 (90 per cent). Bronchoscopic

*A moderate smoker is arbitrarily defined as one who average one to two packages daily for at least 20 years. A heavy smoker is one who averages two packages or more daily for at least 10 years.

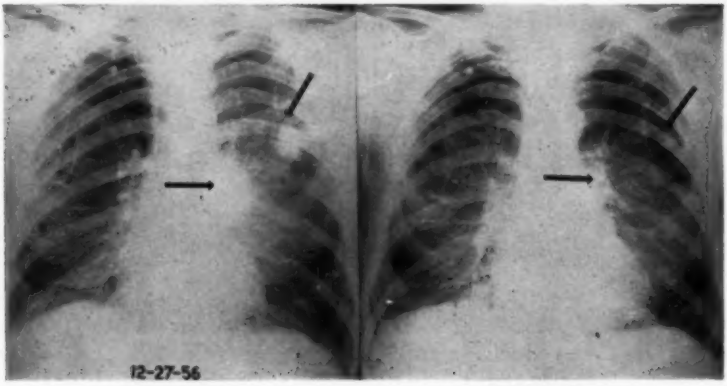

FIGURE 6 FIGURE 7

examinations were performed in 19 patients and gross positive findings were observed in two instances. There was histological confirmation (ante mortem or post mortem) of malignancy in 16 patients and all showed the squamous cell type. In the remaining four, the clinical and roentgenological findings were overwhelmingly consistent with the diagnosis of primary bronchogenic cancer.

The clinical response to therapy is summarized in Tables 1 and 2. Table 3 summarizes survival data in both treated groups and Table 4 relates to the incidence of toxicity and its manifestations.

(1) *Subjective Manifestations:* The improvement in the symptomatology of patients treated with colchicine alone was not significant and of short duration (an average of about two months). It is possible that supportive therapy alone may have contributed to or indeed accounted for these temporary results. (See Table 1).

Superior symptomatic improvement was seemingly obtained in the colchicine-irradiated group. (See Table 2). It is our opinion that the administration of x-ray therapy may have been the most important single factor to account for this difference between the two groups. The ancillary adreno-cortical and androgenic steroid supplements might also have contributed favorably to the results.

(2) *Objective Manifestations:* One must utilize caution in ascribing regressive changes in chest x-ray findings to a specific anti-tumor modality. Experience indicates that when secondary obstructive pneumonitis or suppuration distal to the bronchial carcinoma contributes to the observed roentgen shadow, regression may occur simply with antibiotic therapy (albeit temporary) and lead to an inaccurate evaluation. It is for this reason that such an evaluation is best made by focusing attention on the fate of isolated circumscribed lesions in which the inflammatory component is likely minimal or non-existent. In the group treated with colchicine alone, moderate regression in size of such metastatic lesions was noted in one patient for a period of about three months (case 2). Among the group II cases, considerably regression occurred in a similar type density shortly after the use of colchicine and further

TABLE 4—TOXICITY

	Group 1 (Colchicine)		Composite Groups 1A and 1B	Group 2 Colchicine and X-ray
	1A	1B		
Cases	5	5	10	10
Colchicine (average dose mg.)	18	32.8	25.4	18 (2000-3000 r. each port) (6 had 3 ports) (4 had 2 ports)
Peripheral Blood Ct. depression	none	2 (severe)	2 (severe)	1 (mild)
G.I. Toxicity	1 (mild)	1 (severe) 1 (mild)	1 (severe) 2 (mild)	1 (severe) 1 (mild)
Hematuria	none	none	none	none
Total Toxicity	1 (mild)	3 (severe) 1 (mild)	3 (severe) 2 (mild)	1 (severe) 2 (mild)

DEFINITION: Severe reaction — Platelet count below 100,000 and/or leucocyte count below 1500; diarrhea, vomiting or other gastro-intestinal symptoms difficult to control with conventional medication.

significant improvement was maintained for at least six months after x-ray therapy was instituted (case 3). One patient (case 4) showed marked reaeration of a massive density in the right lung in association with x-ray, colchicine and antibiotic therapy from distant metastases. Another patient in group II revealed definite regression of a large left sided para-mediastinal and hilar density over a period of about two months, but with progression of right sided metastatic lesions. Finally, one patient exhibited moderate roentgen regression of a large right upper lungfield density with similar therapy but progression of a contralateral hilar shadow. The remainder of the six cases in group II revealed no evidence of improvement on the chest x-ray film. In summary, a total of five cases (one in group I and four in group II) showed at one time or another, regressive radiological changes.

(3) *Length of Survival:* The effect of the palliative therapy on length of survival is visualized in Table 3. In the evaluation made September, 1958, nine patients in group I and eight in group II were dead. The single living patient in group I is alive 15 months from the onset of treatment and the similar data for the two living cases in group II is 15 and 20 months. It should be mentioned that one of the two living patients in group II had a lobectomy for his carcinoma, but was relegated to the palliative regimen when post-operative histologic examination of removed tissue indicated extension of the malignancy. Now, 15 months later, he has symptoms and signs of cerebral metastasis.

(4) *Toxicity:* Observed toxicity was confined to gastro-intestinal symptomatology and peripheral blood count depression. The platelet and leukocyte counts were affected more adversely than the red blood cells. It is seen that most of the untoward reactions occurred among the patients who received the heaviest assault with colchicine (group 1B).

Case Reports

Case 1 (Group 1B): G.D'E, white man, age 70, was admitted September 11, 1957 with duration of symptoms from the onset to the beginning of colchicine treatment of about 12 months. Gross bronchoscopic findings were negative. Cytological studies of sputum and bronchial secretions were positive for malignant cells. The chest x-ray film of September 12, 1957 (Fig. 1) showed a density in the right hilar region which was localized in the lateral view in the upper lobe; several calcific foci were also noted in the hilum. He was considered inoperable and colchicine was begun on September 16, 1957—2 mg. intravenously three times weekly for four weeks, then 2 mg. twice weekly for four weeks and finally once weekly for four weeks. He received a total of 48 mg. within a period of 12 weeks without clinical or hematological evidence of toxicity. During the course of treatment, he stated he "felt better" and showed a weight gain of six pounds. However, during colchicine therapy and thereafter, progressive enlargement of the roentgen density was noted (Fig. 2). He died February 21, 1958, about 2 months after colchicine was stopped. An autopsy revealed squamous cell carcinomatous infiltration of the right lung with widespread metastases. Although no major clinical improvement occurred, it is noteworthy that he was able to tolerate 48 mg. of colchicine within a 12 week period.

Case 2 (Group 1B): P.M., a white man, age 51, was admitted on April 16, 1957, with symptoms of two months duration. He appeared chronically ill, dyspnoeic, with enlarged liver and bilateral dependent edema. A chest roentgenogram, just prior to this admission and dated April 5, 1957 (Fig. 3) revealed densities in the left lung field (parenchymal plus pleural components of the primary malignancy), and two discrete rounded shadows (metastases) measuring 1.5 to 2.0 cm. in diameter in the right lung. The first thoracentesis (left) yielded serous fluid from which tubercle bacilli were reported on smear. He was started on appropriate antituberculosis chemotherapy, although bacteriological confirmation was not obtained either from the aspirations subsequently performed or from the sputum. Bronchoscopic examination was grossly negative, but cytological examination of the sputum and bronchial secretions were positive for malignant cells. During hospitalization, cervical nodes became apparent and biopsy revealed squamous cell carcinoma.

He received 16 intravenous injections of colchicine (total 46 mg.) between April 25, 1957 and October 7, 1957. The administration of colchicine was at times postponed because of severe depression of the total leukocyte count and the platelets. The lowest recorded white blood cell count was 1700 and the platelets 60,000. No bleeding episode occurred. Antibiotics and five blood transfusions were given with improvement in the blood picture. On April 15, 1957, 0.5 mg. of colchicine was instilled into the left pleural cavity following a thoracentesis. There was noted an increase in pleuritic pain and pleural fluid immediately thereafter and another aspiration was performed on April 16, 1957. Subsequently, for about a two month period there appeared to be a retardation in the re-accumulation of fluid.

For a better appraisal of roentgenological changes which might be influenced by colchicine therapy, attention was concentrated particularly on the right sided lesions in the frequent serial films. An x-ray film of May 3, 1957 (Fig. 4) revealed moderate regression of these foci compared to the film of April 5, 1957 and this status was maintained for about two months. The last film of October 25, 1957 (Fig. 5) revealed an increase in size in the right mid-lung lesion and new lesions in the upper lobe were observed. He resumed a progressive downhill course; paralysis of the left recurrent laryngeal and phrenic nerves with increased left sided effusion were noted and he died on November 28, 1957.

Case 3: J. K. (Group 2A), a 56 year-old white man was admitted on December 27, 1956 with symptoms of one year's duration. The first x-ray film on December 27, 1956 (Fig. 6) showed calcified foci and some linear pleural (?) folds on the right with an increased density in the left hilum and a more or less circumscribed dense area overlying in part the fourth left anterior rib. Bronchoscopy was negative, but cytological examination of the sputum and bronchial secretions revealed cancer cells. Gantrisin was started on admission and penicillin on January 29, 1957. Colchicine therapy was begun on January 7, 1957 in the dosage of 2 mg. once weekly for three consecutive weeks. X-ray therapy was initiated February 8, 1957 and completed March 11, 1957 with 2800 r delivered over three ports. A second similar course of colchicine was begun on April 1, 1957. No clinical or hematological evidence of toxicity were observed during this regimen. He stated he felt much better, cough decreased, dyspnoea improved with a weight gain of 12 pounds from the onset of therapy to the time of his discharge three months later. Significant radiological regression is seen on the film of January 22, 1957 (Fig. 7) *during* colchicine administration and *before* irradiation was started. Further slight regression was observed on the plate of March 14, 1957 (Fig. 8). He was followed in the out-patient clinic. The film of July 19, 1957 (Fig. 9) (six months later) revealed a marked increase in the original hilar density, although the smaller satellite density (probably metastatic) was only faintly visible. For the past nine months, he has resided in another state. Recent communication with his private physician disclosed that he has shown slow, but progressive clinical deterioration.

Case 4: W. H. (Group 2B), a 51 year-old white man was admitted March 4, 1957 with symptoms dating back for a 10 month period. Fatigability, weight loss, dyspnoea and wheezing were the dominant symptoms. On admission, he was poorly nourished. There was marked dullness with diminished breath sounds over the greater portion of the right lung. The first chest film taken March 6, 1957 (Fig. 10) showed an extensive density involving approximately the upper two-thirds of the right lung. Bronchoscopy revealed the carina to be irregular, thickened and distorted. However, bronchial and scalene node biopsies were negative for malignancy. Cancer cells were found in study of the sputum. X-ray therapy was started April 1, 1957 and completed May

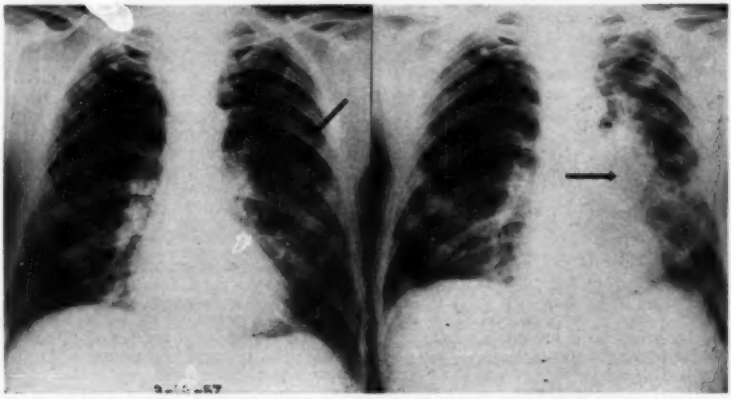

FIGURE 8

FIGURE 9

3, 1957 with 2600 r given over each of three ports. Colchicine therapy was started April 15, 1957 in the dosage of 4 mg. intravenously given once weekly for three consecutive weeks. He received a total of 12 mg. with no clinical or laboratory sign of toxicity. He noticed decreased exertional dyspnoea, cough and wheezing. This improvement, which lasted for about two months, became apparent soon after irradiation was begun. His clinical status thereafter declined; the liver became considerably enlarged with the development of ascites and jaundice. He died on August 30, 1957. Of interest is the fact that there was marked roentgen reaeration (Fig. 11) of the original density (which may have been due largely to atelectasis) as late as on the last film taken July 15, 1957. This improvement might be attributed mostly to x-ray therapy, although he also received colchicine, antibiotics and steroids.

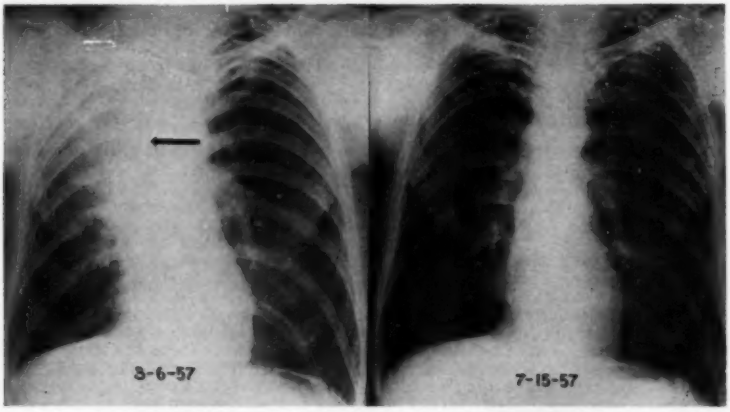

FIGURE 10 FIGURE 11

Comment

It has been amply demonstrated that colchicine arrests cellular division in the stage of metaphase.[20,28] Colchicine is one of a number of agents (physical and chemical) which may interfere with mitosis. Both normal and malignant cells are similarly affected, but cells with the greatest rate of division and metabolism are hit earliest by colchicine.[15] The optimum duration of a given dose of colchicine varies with the species of animal studied. Levine and Silver[9] concluded from their observations that the greatest arrest of nuclear division in the metaphase occurred between 16 to 24 hours, in human cancer cells.

The effect of colchicine on the normal polarized "spindle" is to convert it into an amorphous mass with distortion of its fibrillar structure and disruption of the movements of the chromosomes. Recently, Laster and Blair have indicated that colchicine inhibits the enzyme uric acid riboside phosphorylase.[29] However, further investigation is necessary to identify the chemical locus of action of colchicine.

It has been demonstrated in experimental animals that colchicine also induces temporary regression of tumor growth by damage to its vascular supply, thereby inducing hemorrhage and necrosis. The endothelial cells of newly formed capillaries are particularly sensitive to mitotic poisons.[19,28]

X-ray irradiation, like colchicine, disrupts nuclear division and damages newly forming capillaries; however, a true synergistic action between irradiation and colchicine, although postulated, has not been conclusively demonstrated.[15] Lettre,[22] in conducting experiments in fibroblast cultures, discovered many agents which increased the mitotic inhibitory activity of colchicine, although themselves having no such mitotic action. Among these synergists are the steroid hormones. For a comprehensive review and evaluation of the many experimental studies with colchicine on cellular physiology, the interested reader should refer to the excellent monograph by Eigsti and Dustin.[30]

Recent interest in the clinical efficacy of colchicine as a chemotherapeutic agent in human malignancy has been stimulated by Isch-Wall,[31] and Grollman, et al.[27] The latter administered the drug in the dosage of 3 mg. intravenously every third day for variable periods to 10 patients with Hodgkin's disease, some of whom were resistant to x-ray therapy and nitrogen mustard. Potent antipyretic and analgesic effects, with marked subjective improvement were obtained. Temporary reduction of enlarged nodes was evident in some cases. The drug was well tolerated.

Despite its equivocal efficacy from our present study, we are continuing to employ colchicine as another tool in the chemotherapeutic attack on inoperable bronchogenic

carcinoma. The dosage currently used is 2 mg. for patients 130 pounds or under, and 4 mg. for patients above that weight. This is an empirical decision based on our clinical experience to date. The drug appears well tolerated in this dosage and can be given one to three times weekly, depending on whether it is used singly or in combination with other modalities. Weekly blood counts, including platelet counts, are essential for proper guidance as to possible bone marrow inhibition, which may require reducing the dose, postponing, or terminating therapy. The availability now of a safe and acceptable intravenous preparation of colchicine warrants, in our opinion, further trial of its use, preferably in conjunction with other modalities, in palliative therapy.

SUMMARY

The marked rise in the incidence of cancer of the lung accentuates the importance for its early detection. Unfortunately, since most instances of this type of malignancy seen today are inoperable, the burden of management rests on a medical palliative regimen. A vigorous search for chemotherapeutic agents is being maintained.

There have been extensive exprimental studies with colchicine. It exerts: (1) a cytotoxic effect by inhibiting spindle formation and arresting cell division in the metaphase stage and (2)an anti-tumor effect by destroying the endothelial cells of newly formed capillaries thereby inducing hemorrhage and necrosis.

Colchicine has received comparatively little attention in its application to human cancer chemotherapy. The availability of an intravenous preparation prompted the present clinical study. Ten patients with advanced bronchogenic carcinoma were treated with colchicine and an equal number with colchicine combined with the conventional type of irradiation and associated medication. It is noteworthy that large amounts of colchicine administered intravenously were well tolerated by most of the patients. The subjective and objective manifestations of improvement in both groups are recorded. The colchicine - x-ray treated group seemingly fared better but this could possibly be due to the effects of radiotherapy per se.

It is necessary to continue to explore many modalities. Colchicine may merit further application as another tool in conjunction with other currently used measures in the palliative regimen.

RESUMEN

Se han hecho amplios estudios experimentale de la colchicina en el cáncer del pulmón.

Ella ejerce: (1) un efecto citotóxico al inhibir la formación fusiforme de acromatina y detención de la división celular en el estado de metafase, y (2) un efecto antitumoral destruyendo las celdillas endoteliales de los capilares neoformados, lo que conduce a hemorragia y necrosis.

La colchicina ha recibido comparativamente posa atención en su aplicación al hombre en quimioterapia del cáncer.

La posibilidad de contar con un preparado para uso intravenoso, condujo a hacer este estudio. Diez enfermos can cáncer avanzado bronquiogénico, se trataron con colchicina en combinación con los métodos habituales de irradiación y tratamiento médico. Es de notarse que grandes cantidades de colchicina administradas intravenosamente, se toleraron bien por la mayoría de las enfermos. Se relatan las manifestaciones subjetivas y objetivas de mejoría en ambos grupos.

Al parecer los tratados con colchicina y rayos X, evolucionaron mejor, pero esto puede deberse a la radiación por sí sola.

Es necesario continuar explorando muchas modalidades. La colchicina puede merecer aplicaciones més adelante como un instrumento más, agregado a las medidas paliativas actuales.

RESUMÉ

Des études expérimentales de la colchicine dans le cancer du poumon ont été faites sur une large échelle. Il en ressort: 1°) qu'il existe un effet cytotoxique par inhibition de la formation des fuseaux et arrêt de la division cellulaire dans le stade métaphasique; 2°) un effet antitumoral par destruction des cellules endothéliales des capillaires nouvellement formés entrainant ainsi l'hémorragie et la nécrose.

La colchicine a peu attiré l'attention dans l'ensemble de la chimiothérapie anticancéreuse chez l'homme. La mise à la disposition des auteurs d'une préparation intraveineuse accélère la possibilité de cette étude clinique. Dix malades atteints de cancer bronchique avancé furent traités par la colchicine et un nombre égal de malades avec la colchicine associée au type habituel d'irradiation et à la médication associée. Il faut noter que des doses importantes de colchicine furent administrées par voie intraveineuse et bien tolérées par la plupart des malades. Des manifestations subjectives et objectives d'amélioration dans les deux groupes ont été constatées. Le groupe de malades traités par la colchicine et les rayons X sembla se porter mieux mais ceci pourrait peut-être être dû aux effets de la radiothérapie seule.

Il est nécessaire de continuer à explorer toutes les modalités. La colchicine peut justifier des applications ultérieures comme un moyen supplémentaire susceptible d'être associé à ceux qui sont couramment utilisés dans le traitement palliatif du cancer.

ZUSAMMENFASSUNG

Es wurden ausgedehnte experimentelle Untersuchungen angestellt mit Colchicin. Colchicin bewirkt: 1) einen cystofischen Effekt durch Hemmung der Spindelbildung und der Zellteilung in der Metaphase; 2) einen Anti-Tumor-Effekt durch Zerstörung der Endothelzellen von neugebildeten Kapillaren mit nachfolgender Hämorrhargie und Nekrose.

Colchicin hat vergleichsweise geringe Aufmerksamkeit erfahren hinsichtlich seiner Anwendung in der menschlichen Krebstherapie. Die zur Verfügungstellung eines intravenösen Präparates veranlaßte die vorliegende klinische Untersuchungsreihe. 10 Kranke mit fortgeschrittenem Bronchoskarzinom wurden mit Colchicin behandelt, und eine gleiche Zahl mit Colchicin in Verbindung mit der üblichen Bestrahlung und der damit verknüpften internen Therapie. Es ist bemerkenswert, daß beträchtliche Mengen von Colchicin-intravenös verabfolgt von den meisten Kranken gut vertragen wurden. Die subjektiven und objektiven Äusserung en der Besserung in beiden Gruppen wurden aufgezeichnet. Die mit Colchicin und Röntgenstrahlen behandelte Gruppe schien besser Garant zu sein; aber dies konnte auch möglich sein infolge der Wirkung der Röntgenstrahlen allein.

Die Fortsetzung der Erforschung vieler Anwendungsmöglichkeiten ist notwendig. Colchicin sollte weitere Anwendung verdienen als ein weiteres Werkzeug in Verbindung mit anderen laufend angewandten palliativen Maßnahmn.

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Tuberculous Peritonitis: A Review of 34 Cases with Emphasis on the Diagnostic Aspects*

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Our interest in this subject was stimulated by the review, made by one of us (J.E.G.) and colleagues,[1] of the cases of fever of undetermined origin encountered at the Mayo Clinic in which exploratory laparotomy was finally necessary for diagnosis. We were surprised to discover that five of the 70 cases of obscure fever in that series proved on laparotomy to be cases of tuberculous peritonitis. Since the diagnosis of tuberculous peritonitis was not suspected preoperatively, it seemed worth while to analyze our cases of proved tuberculous peritonitis particularly from a diagnostic standpoint. Scant attention has been given this aspect of tuberculosis in the recent literature, and no mention of tuberculous peritonitis presenting as obscure fever could be found, although Keefer and Leard[2] did discuss the problem of tuberculosis in general as a cause of obscure fever.

Analysis of Study

One hundred twenty-four cases of tuberculous peritonitis were encountered at the clinic from 1940 through 1958. This is a smaller number than the 409 cases encountered in a 2-year period and reported on in 1929.[3] After careful review only 34 of the present series were diagnostically acceptable on the basis of guinea pig tests positive for tuberculosis. The remaining 90 were excluded because the diagnosis was made only on the basis of a positive culture or from microscopic examination of biopsy material without the benefit of guinea pig inoculation. Weed[4] has emphasized that there are strains of acid-fast bacilli whose colonies are identical to those of Mycobacterium tuberculosis and that diagnosis of tuberculosis depends finally on the results of virulence tests on guinea pigs. Most of the other reported series referred to herein have not required positive findings on virulence tests for diagnosis.

Clinical and Laboratory Observations and Surgical Procedures in 34 Cases

Age and Sex — Tuberculous peritonitis has no preference for either sex. It appeared to affect females predominantly in some large series[5,6], but these series were weighted with a large number of patients with tuberculous salpingitis. There were 19 males and 15 females in our group. Youth has frequently been emphasized as the most common age for tuberculous peritonitis; but 20 of our patients were more than 40 years of age.

Symptoms — Mild abdominal pain has often proved to be the first indication of tuberculous peritonitis.[7,8] However, the symptoms are varied,

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TABLE 1 — SYMPTOMS AND CHIEF COMPLAINTS OF 34 PATIENTS

Symptoms	First symptom	Chief complaint
Fatigue and malaise	11	13
Abdominal pain	9	7
Abdominal swelling	6	9
Abdominal tenderness	3	
Fever	2	3
Conspitation	2	
Diarrhea	1	
Nausea		1
Abdominal fistula		1

and no one symptom or sign can be relied on as diagnostic. The first symptoms and those mentioned as the chief complaint by our patients are listed in table 1.

In all but two of our cases the onset of symptoms was gradual or insidious. Only seven patients had had symptoms for less than 2 months at time of examination at the clinic; seven had had symptoms for 2 to 4 months; 13 for 4 to 6 months and seven for longer than 6 months. None could be classed as having acute tuberculous peritonitis.

The symptoms noted in our cases are compared with those of other series reported in the last 50 years in table 2. The differences in the frequency with which certain symptoms occurred in the various series appear significant. These result in part perhaps from selection of patients in the different series. Table 2, however, does emphasize the wide variety of nonspecific symptoms noted in this illness.

Of our 19 patients with fever, 13 had temperatures between 99° and 102° F. on examination at the clinic, and none had temperatures of more than 103° F. The classical doughy abdomen associated with tuberculous peritonitis was rather conspicuous by its absence in most of our cases. On exploratory laparotomy, the palpable masses usually were found to be rolled omentum. Ascites was never massive. Adams[14] has emphasized that the fluid associated with peritonitis feels loculated and is not free in the abdomen as in cirrhosis or nephrosis.

It was surprising that we found no additional patients whose clinical picture was that of fever of obscure origin. However, six patients had the clinical syndrome of ascites of obscure origin. Each of these had malaise and mild anorexia, but the cause could not be diagnosed clinically. Kampmeier[15] discussed one patient who presented with watery diarrhea of 8 months' duration. The diarrhea appeared to be due to tuberculous enteritis which was secondary to an essentially asymptomatic tuberculous peritonitis.

Laboratory Studies — The routine laboratory studies have generally not been of aid in diagnosis of tuberculous peritonitis. Leukocyte counts of 4000 to 6000 per cubic millimeter of blood were found in 18 of our patients and counts of more than 10,000 in only two. The sedimentation rate of erythrocytes in 1 hour (Westergren method)) was 0 to 19 mm. in seven patients; 20 to 59 in seven; 60 to 99 in six; and 100 to 146 mm. in six. Only 15 of the 34 patients had albuminuria. In nine of these it was of minimal degree.

TABLE 2 — COMPARISON OF SYMPTOMS AND SIGNS IN OUR 34 CASES OF TUBERCULOUS PERITONITIS AND THOSE IN OTHER SERIES REPORTED IN THE LAST 50 YEARS

	Our series	Kahrs[9]	Wichel-hausen, and Brown[7]	Barrow[10]	Stuben-bord and Spies[11]	McPhedran and Peacock[12]	Faulkner and Everett[8]	Hammon[8]	Diwany and Gabr[13]
Cases	34	169	26	67	257	21	187	150	16
Symptoms, per cent of cases									
Loss of weight	74	25	85	77	19	14	61	41	88
Abdominal swelling	71	45	31		66	42	32	15	75
Abdominal pain	62	76	88	75	72	76	87	69	87
Anorexia	59	27	27		7	28			69
Fever	50	61	92	82	17		76	90	88
Fatigue and malaise	47		19		20	19			
Constipation	29		23		23		42	32	
Night sweats	26		12					18	
Nausea	21		35	32	4		33	34	
Vomiting	19	23	38	32	30	24	27	38	37
Diarrhea	19	27	42		15		7	22	53
Physical signs, per cent of cases									
Distention	68		69	82	61	38	44		
Ascites	65		62	65	35	24	28	42	44
Fever	56		92	82	17		76	90	
Abdominal tenderness	38		65	71	27	43	54	29	56
Palpable liver	26		8		3			11	
Abdominal mass	24		23		27	9		37	56
Palpable spleen	19		4					2	
"Doughy" abdomen	12			10	3	<10			

NONE GIVEN

The concentration of serum proteins and the albumin-globulin ratio were determined in eight patients. Both of these values were normal in six, and the total protein was normal but the ratio was reversed in two. Roentgenograms of the stomach, small bowel and colon were essentially noncontributory.

All 34 patients had roentgenograms of the thorax. The roentgenograms of three patients were read as probably indicating active tuberculosis; of four as probably indicating old pulmonary tuberculosis; and four as showing Ghon complexes. An additional three indicated some lesion not suggestive of tuberculosis. Thus only 11 patients (32 per cent) of our series had any suggestion of pulmonary tuberculosis. At the time of diagnosis of tuberculous peritonitis, an additional three patients had a definite history of exposure to persons with tuberculosis in their immediate family within the previous 2 years.

Of the 18 patients who had tuberculin tests with P.P.D. of first and second strengths, seven reacted positively to the first strength tuberculin, six had negative reactions to the first strength but positive reactions to the second strength P.P.D.; two had negative reactions to the first strength tests and results of the second strength tests were not recorded. In three patients (17 per cent), tuberculin tests gave negative results with both strengths. The infection did not appear to be overwhelming in any of these three patients.

Simple paracentesis with examination of the fluid for acid-fast bacilli by smear, cultures and guinea pig inoculation was performed on only four patients. In an additional nine, fluid for smear, cultures and inoculation of guinea pigs was obtained at laparotomy. Smears of fluid were negative for tuberculosis in all 13 cases. The cultures were positive in only five of these 13, but the results of guinea pig inoculation were positive in all 13.

Peritoneoscopy was performed on four of our patients. It was successful in three, and no true peritoneal cavity could be located because of adhesions in the fourth. Tissue obtained at the time of the three successful peritoneoscopic procedures revealed tuberculosis on guinea pig inoculations.

Laparotomy — The diagnosis was made at exploratory laparotomy in 26 of the 34 patients. The surgical findings are tabulated in table 3.

TABLE 3 — SUMMARY OF GROSS FINDINGS AT LAPAROTOMY

	Per cent of cases		
Gross findings	Our group (26 cases)	Wichelhausen and Brown[7] (21 cases)	Stubenbord and Spies[11] (171 cases)
Tubercles	69	71	62
Adhesions	23	48	29
Free fluid	23	33	42
Caseous nodes	8	29	10
Thickened peritoneum	9	5	9

The tubercles were usually described as multiple, grayish-yellow nodules, measuring 1 to 3 mm. In those cases with excessive ascitic fluid (wet type) the exudate covering the peritoneum appeared to be more fibrinoid, the adhesions fewer and more delicate, and the bowel more

pliable. The dry types consisted of large nodular tubercles, a heavy gelatinous exudate and loculation of any fluid present. Adhesions were present, and the intestinal wall was more plastic.

Histologic Findings — Specimens of tissue were obtained in 31 cases by means of laparotomy, peritoneoscopy and liver biopsy (one case). The histologic diagnosis was caseous granuloma consistent with tuberculosis in all 31.

Pathogenesis of Tuberculous Peritonitis

Tuberculous peritonitis is always secondary to some other primary tuberculous lesion. However, as emphasized by Nice,[16] the primary site in the lung can heal completely after hematogenous spread. Tuberculous peritonitis also can result from local spread from caseous mesenteric nodes, intestinal tuberculous ulcer and tuberculous salpingitis. Primary intestinal tuberculosis[17] became practically extinct in this country following the passage of cattle inspection laws by Congress in 1906. The Novaks[18] stated that most tuberculous salpingitis is caused by hematogenous spread from the lung. By the nature of the anatomy, once tuberculous salpingitis develops, tuberculous peritonitis in some degree is almost certain to follow. Brown and associates[5] noted tuberculous peritonitis in 141 of 152 patients with pelvic tuberculosis who were studied at Johns Hopkins Hospital. Salpingitis was present in only four of our cases.

Diagnosis

Tuberculous peritonitis should be considered whenever a patient has fever, abdominal pain and tenderness, ascites, and loss of weight, and when a roentgenogram of the thorax is suggestive of tuberculosis. The symptom complex of abdominal swelling, abdominal pain and fever with loss of weight and anorexia also should be highly suggestive. Of these symptoms, abdominal swelling is the most localizing and best clue. This may be mentioned by the patient as postprandial fullness or he may complain of difficulty in fastening his clothes. The real problem in diagnosis occurs when some of these typical signs and symptoms are absent and the chest is clear. Twenty of our patients appeared to have tuberculosis limited to the peritoneum without obvious evidence of tuberculosis elsewhere. The diagnosis of tuberculous peritonitis was mentioned initially as the most likely diagnosis in six of our cases and as a possibility in an additional four cases. The suggested probable diagnoses or initial impressions made by the physicians after the history and physical examination in our cases were cancer or lymphoma in nine cases, tuberculous peritonitis in six, cancer or tuberculous peritonitis in four, cirrhosis with ascites in three, cirrhosis or malignancy in two, irritable bowel in three, cholangitis and intestinal obstruction in one each and indeterminate in five.

Abdominal carcinomatosis frequently is associated with a distended abdomen, but often the liver will be found to be enlarged, firm and nodular. Although the liver was palpable in 26 per cent of our cases, it was definitely enlarged in only one case and in that case amyloidosis was a secondary finding. Hodgkin's disease may be limited to the abdo-

men and may simulate tuberculous peritonitis closely. Bennett[19] reported two interesting cases in which the clinical diagnosis was tuberculous peritonitis but in which the diagnosis later proved to be carcinomatosis and lymphoma respectively.

Disease states in which ascites frequently occurs are cirrhosis of the liver, the nephrotic syndrome, congestive heart failure, and obstruction of the portal or hepatic vein. Pseudomyxoma peritonaei[20], although rare, should be considered in the differential diagnosis also. Inasmuch as smears, and cultures of ascitic fluid are frequently negative and guinea pig inoculations almost always are positive for tuberculosis, one should not fail to do guinea pig inoculation tests with the fluid or tissue obtained. Laparotomy is probably the best method of obtaining fluid and tissue for rapid and accurate diagnosis.

Treatment

In 1958 the Committee on Chemotherapy and Antibiotics of the American College of Chest Physicians[21] suggested the following regimen for the treatment of tuberculosis: isoniazid, 300 mg. daily, plus para-aminosalicylic acid (PAS), 12.0 gm. per day, or 300 mg. of isoniazid daily plus 1.0 gm. of streptomycin twice a week or a combination of all three drugs in these dosages. However, a recent summary of the Eighteenth Veterans Administration Armed Forces Conference[22] on the chemotherapy of tuberculosis indicates that the first two regimens are equally as effective as the third or triple drug regimen and that the incidence of drug toxicity is greater with the last regimen.

The place of steroids combined with these drugs in the treatment of tuberculosis has not been settled. The work of Ilavsky and Foley[23] with cortisone plus isoniazid in experimental tuberculous peritonitis showed that the combination was at least no worse than isoniazid alone. However, streptomycin with cortisone appeared to give less favorable results. Wichelhause and Brown[7] reported that 25 of 26 patients with tuberculous peritonitis treated with streptomycin in various Veterans Administration hospitals over the country in 1948 responded favorably. In a later report of 70 additional cases of tuberculous peritonitis treated in Veterans Administration hospitals, Rothstein[24] expressed disappointment. His results were: cured 44 per cent, improved 40 per cent, unchanged 4 per cent, worse 12 per cent. Eight per cent later relapsed after apparent cure or improvement and 11 per cent of the total group died. This Veterans Administration pilot study was discontinued the following year, in 1951. Diwany and Gabr[12] reported cures in 13 (80 per cent) of 16 children treated for tuberculous peritonitis with dihydrostreptomycin. Satisfying results also have appeared in other reports consisting of one or two cases.[25-28]

Results of Treatment

Of our 34 patients one has been lost to follow-up and 11 have died. Of the 22 who are still living all but one has been followed for 4 years. The one exception has been followed for only 12 months as yet. The results of treatment in our cases are summarized in table 4. The type of chemotherapy was too varied and the series is too small to permit any deductions with regard to the best treatment regimen.

TABLE 4 — TREATMENT AND RESULTS

Treatment				Results				
					Died from:			
Drug	Average dose given	Duration, mo.	Total patients	Living and well	Relapse	Tuberculosis	Unrelated cause	Lost to follow-up
Streptomycin, PAS* and isoniazid	3.0 gm./week 12-16 gm./day 300 mg./day	1 only 12	2	1	0	0	1	0
Streptomycin and PAS*	2-3 gm./week 16 gm./day	4-6	12	7	1	1	3	0
Streptomycin and isoniazid	2-3 gm./week 300 mg./day	9	4	4	0	0	0	0
Streptomycin alone	1.0 gm./day	3	4	2	0	0	1	1
Isoniazid and PAS*	300 mg./day 16 gm./day	12	4	2	0	0	2	0
No chemotherapy			8	5	0	3	0	0
Total			34	21	1	4	7	1

*Para-aminosalicylic acid.

Twenty-six of the 34 patients received chemotherapy under the direction of the physicians at the Mayo Clinic; there was only one treatment failure with death due to tuberculosis. This one patient had had proved recurrent tuberculosis for 8 years and abdominal symptoms for 6 months prior to coming to the clinic. He then received streptomycin and para-aminosalicylic acid as recommended for 8 months before death ensued.

Of the eight patients who were seen in the pre-chemotherapeutic era, three died of active tuberculosis, and five recovered without any specific treatment. Mortality figures of large series of treated patients in the pre-chemotherapeutic era have been essentially the same, that is, roughly a 50 per cent mortality rate: Barrow[10] reported 55 per cent, and Shattuck,[29] Brown and assoociates,[5] 47 per cent. The therapeutic results of our series even though small do appear favorable.

Seven of the 11 deaths in the series were due to causes other than tuberculosis. Three patients died within 2 weeks of exploratory laparotomy from pulmonary embolism, pulmonary edema following transfusion and cerebral vascular thrombosis. Two died within a year of acute leukemia, one of diabetic coma and one of alcoholic cirrhosis.

SUMMARY

Thirty-four cases of tuberculous peritonitis, all with a diagnosis proved by guinea pig inoculation, were encountered at the Mayo Clinic from 1940 through 1958. No one diagnostic sign, symptom, routine laboratory finding or syndrome characterized this type of tuberculous infection. However, in five cases the condition presented as fever of obscure origin and in six as ascites of obscure origin. Laparotomy and to a lesser degree peritoneoscopy with smears, cultures and guinea pig inoculations of the specimens removed provided a rapid and accurate method for certain diagnosis. The results of treatment of this series are outlined, but the therapeutic data of the several regimens used were too meager to justify any definite conclusions.

RESUMEN

En le clínica Mayo se encontraron desde 1940 hasta 1958 treinta y cuatro casos de peritonitis tuberculosa, todos con diagnóstico comprobado por inoculación al cuy. Ningún signo diagnóstico, síntoma, hallazgo de rutina de laboratorio o síndroma, fué característico de esta forma de infección tuberculosa. Sin embargo en cinco casos, la enfermedad presentó fiebre de origen desconocido y en seis hubo ascitis de origen obscuro. La laparotemía y en grado menor la peritoneoscopia con frotis, cultivo e inoculación al cuy de los especímenes extraídos proporcionarón un método rápido y exacto de diagnóstico. Se describen los resultados de tratamiento de esta serie, pero los datos terapéuticos de los varios regímenes usados, fueron muy escasos para justificar conclusiones definitivas.

RESUMÉ

Trente-quatre cas de péritonite tuberculeuse, tous mis en évidence par inoculation au cobaye, ont été suivis à la Clinique MAYO de 1940 à 1958. Aucun élément de diagnostic tiré de la symptomatologie ou des constatations bactériologiques courantes ne caractérisa ce type d'infection tuberculeuse. Cependant, dans cinq cas, il y avait une fièvre inexpliquée et dans six une ascite d'origine obscure. Une laparotomie et à un moindre degré une péritonéoscopie avec frottis, cultures et inoculations aux cobayes des fragments prélevés fournit une méthode rapide et précise pour un diagnostic certain. Les résultats du traitement de cette série sont esquissés, mais les données des différentes méthodes thérapeutiques utilisées sont insuffisantes pour justifier toute conclusion définitive.

ZUSAMMENFASSUNG

In den Jahren von 1940 bis Ende 1958 wurden an der Mayo-Klinik 34 Fälle von tuberkulöser Peritonitis gezählt; in allen Fällen war die Diagnose durch Tierversuch am Meerschweinchen gesichert. Kein einziges diagnostisches Kriterium, Symptom oder einer der routinemässigen Laborbefunde oder ein sonstiges Syndrom kennzeichnete diese Art der tuberkulösn Infektion. In 5 Fällen zeigte die Affektion jedoch Fieber unklarer Herkunft und in 6 Fällen Ascites unklarer Genese. Die Laparotomie und in etwas geringerer Gr[illegible] die Bauchspiegelung mit Ausstrichen, Kulturen und Tierversuch aus ertnom [illegible]aterial führen als rasche und genaue Methoden zu einer sicheren Diagnose.

Die bei diesem Krankengut erzielten Behandlungsergebnisse werden mitgeteilt; jedoch waren die therapeutischen Werte bei den benutzten verschiedenen Heilverfahren zu kärglich, als dass man endgültige Folgerungen daraus zu ziehen berechtigt wäre.

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Reversion and Reconversion Rate of Tuberculin Skin Reactions in Correlation with the Use of Prednisone[1,2]

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The cutaneous tuberculin sensitivity found in healthy persons who have had a tuberculous infection, or in sufferers from tuberculosis, or in experimental animals previously sensitized with BCG or heat-killed tubercle bacilli, is usually inhibited or diminished by certain agents including adrenocorticotrophic hormone and adrenal corticosteroids, administered either systemically or locally.[1-13]

Our present study is based on a sizable group of natural tuberculin converters who received prednisone at random or as a trial treatment for certain forms of tuberculosis for a varying period until at least the reversion of skin sensitivity was definitely obtained. The primary purpose is to record the exact time of inhibition of tuberculin sensitivity with the use of corticosteroid in the same dosage and also the time of reconversion of the reaction after withdrawal of treatment.

Materials and Methods

From December, 1957 to May, 1959, 70 tuberculin reactor patients were studied. There were 40 men and 30 women, with age ranging from 14 to 80 years. Fifty-eight of them were under treatment for tuberculous diseases, and 12 suffered from other conditions but gave positive tuberculin tests.

In all cases, the intradermal tests with 5 T.U., P.P.D. tuberculin were performed at the beginning of the study. These were usually done in duplication. Each test was read at the end of 72 hours. The reactions were recorded in millimeters of erythema and induration; positive tests being of 5 millimeters of induration and over. Where the initial tests were positive, the corticosteroid was immediately started. Thereafter, in each case, the same intradermal test was repeated at 72 hour intervals during treatment and after, until the tuberculin reaction again became positive. The reversion rate in days is reckoned on the first reading of two consecutive negative tuberculin tests from the day after corticosteroid was first given. Likewise, the reconversion rate, is based on the return of positive tuberculin reading from the day after corticosteroid was stopped.

Prednisone, under the trade name of Meticorten, supplied by the Schering Corporation, Bloomfield, New Jersey, was used throughout the study. It was given by mouth in a rigid dosage of 10 milligrams (two 5 mg. tablets) six hourly in all cases. The duration of treatment varied according to the group: those under a study program of treatment for tuberculosis received the steroid for a period of one month, the remainder until the second consecutive negative tuberculin test. All patients received intramuscular streptomycin 1 gram once daily and isoniazid 300

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[2]Presented at the monthly meeting, Siriraj Hospital.

to 400 milligrams daily in three or four divided doses concomitantly with the steroid.

In addition, five tuberculous, one bronchogenic carcinoma and two sarcoid patients who initially gave negative tuberculin test were included in the study. They all received a one-month course of prednisone.

Results

A. *Study of 70 tuberculin positive patients:—*

Initial Tuberculin Reactions:

	Mean value in mm.	
	Erythema	Induration
40 men	15.9±6.4	14.1±4.9
30 women	18.1±9.9	14.4±6.7
Total 70 cases	16.8±10.8	14.2±7.6

The size of skin reactions did not correlate with sex, age, or activity of the tuberculous infection. There is no constant proportion between the size of erythemas and indurations.

Reversion Rate:

Of the 70 patients, 68 showed complete inhibition of tuberculin skin sensitivity at some time along the course of prednisone. Two men (19 and 27) had not reached the stage of tuberculin anergy at the end of one-month course of prednisone. In 12 patients, swinging of reactions between negative and positive were observed before actual reversion.

	Mean value in days
38 men	14.8±8.7
30 women	12.0±7.7
Total 68 cases	13.6±10.1

The average time of inhibition of tuberculin sensitivity with the use of prednisone in this series is 13.6±10.1 days. There was also no correlation between the tuberculin reversion rates and the sex, age, activity of infection or the severity of initial skin reactions.

Most of the patients showed decreased sensitivity during administration of prednisone. There were however four cases in each of which an increase in sensitivity occurred (Table 1).

TABLE 1—SIZE OF TUBERCULIN REACTION BEFORE, DURING AND AFTER PREDNISONE

Name	Before	Induration in mm. in successive tests During Prednisone Adm.										After	
		1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	1st	2nd	3rd
V.Sv.	6	0	0	0	0	0	0	0	8	20	22	25	20	18
K.L.	10	8	15	3	0	0	0	0	0	0	0	8	8	
H.H.	18	20	0	0	0	0	0	0	0	0	0	0	15	16
O.S.	5	8	0	0	0	0	0	0	0	0	0	0	6	8

Reconversion Rate:

	Mean value in days
38 men	6.9±3.6
30 women	5.0±2.6
Total 68 cases	6.0±3.3

The overall mean reconversion rate is 6.0±3.3 days. The difference of results in the men and the women is of statistical significance. The correlation between the tuberculin reconversion rates and the age, activity

of infection or severity of initial reactions was also not obtained.

B. *Study of eight tuberculin negative patients*:—

TABLE 2—EFFECT OF PREDNISONE ON TUBERCULIN REACTION OF INITIALLY TUBERCULIN NEGATIVE CASES

Name	Sex	Age	Diagnosis	Initial Tbn. mm. Eryth.	Indur.	Convers. Rate days During	After
F.N.	M	21	Tbc. pulmonary	0	0	—	—
P.Pr.	M	56	Tbc. pleural effusion	0	0	—	
P.T.	F	22	Tbc. miliary	0	0	—	
L.U.	F	59	Tbc. miliary	0	0	—	—
Ch.S.	F	61	Tbc. pleural effusion	0	0	—	—
N.Y.	F	49	Bronchogenic carcinoma	0	0	—	9
P.T.	F	17	Sarcoidosis	0	0	—	—
R.Ch.	F	30	Sarcoidosis	0	0	—	—

Discussion

The results obtained by previous investigators on the relationship of the tuberculin sensitivity and the application of corticosteroids vary widely. A large number of reports show grades of partial inhibition, but a few give total inhibition in some cases. Spain and Molomut (1950),[14] and Coste et al (1951)[15] noted slight increase in size of the reaction during hormonal treatment. These variable results have been explained as being caused by the differences in the dosage and in the duration of administration of the steroid.[2,4,10,11] Most of our patients showed decreased sensitivity during administration of prednisone. In 12 out of 70 cases, there occurred swinging of reactions between negative and positive before actual reversion. Cases 8, 31 and 55 took 39, 57 and 36 days respectively to revert. At the end of one-month course of prednisone which was part of the regime of anti-tuberculous treatment of a group, two cases (19 and 27) had not reached actual reversion. They would probably have reverted had administration of prednisone been continued. There were four unusual cases in each of which an increase in sensitivity occurred.

The time of occurrence of total inhibition of tuberculin sensitivity with the use of ACTH or corticosteroids, and also the time of reconversion to positive reaction after cessation of treatment have not been studied on a large scale. Harris and Harris (1950)[3] found that rabbits and guinea pigs previously sensitized with BCG were rendered negative to tuberculin test within 24 to 48 hours with the steroid treatment and 4 days after cessation of treatment the skin test again became positive. Long and Favour (1950)[2] reported findings in man that with the use of ACTH or cortisone, a return of the sensitivity reaction occurred in each patient tested between seven to 28 days after cessation of treatment. LeMaistre, Tompsett, Muschenheim, Moore and McDermott (1951)[6] found that in two of their patients the reversal of a previously positive response was maintained for three to four weeks after cessation of the hormone administration. The results of the present study of 70 patients are: the average reversion rate 13.6±10.1 days, and reconversion rate 6.0±3.3 days. In comparison with the above the longest reconversion rate was 21 days in one case and next ot this was 15 days in another.

Some cases of tuberculosis and sarciodosis which had previously given negative tuberculin reactions became positive during treatment with corticotrophin or corticosteroids.[9,12,16,17] We have had experience with five tuberculous patients, one bronchogenic carcinoma and two sarcoids. All gave negative readings to 5 T.U., P.P.D. tuberculin before and during administration of prednisone. Some time after a one-month course of prednisone, one of the tuberculous and the bronchogenic carcinoma patient became positive to tuberculin tests. The other four tuberculous cases and the sarcoids repeatedly failed to show conversion.

SUMMARY

The present report is based on 70 natural tuberculin converters who received prednisone during an antituberculosis regime. Intradermal test with 5 T.U., P.P.D. were done at 72 hour intervals before, during and after a course of prednisone.

The original statement of Boquet and Bretey (1934)[18] that there is no correlation between the intensity of the tuberculin reactions and the severity of the tuberculous infections is confirmed.

Our study has shown that with the use of prednisone in an adequate dosage and for an adequate duration the cutaneous tuberculin sensitivity in both active and inactive cases of tuberculosis could be totally inhibited. The mean reversion and reconversion rates are 13.6±10.1 and 6.0±3.3 days respectively.

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RESUMEN

Esta comunicación se basa en la observación de 70 reactores a la tuberculina que recibieron prednisona durante un régimen antituberculoso. La reacción intradérmica con 5 T.U., P.P.D. se hicieron durante y después del curso de la prednisona.

El aserto original de Boquet y Bretey (1934),[18] de que no hay correlación entre la intensidad de las reacciones tuberculínicas y la gravedad de las infecciones tuberculosas, se confirma.

Nuestro estudio ha mostrado que con el uso de la prednisona, en dosis adecuada, la reacción tuberculínica cutánea tanto en casos activos como en inactivos, puede inhibirse totalmente.

La reversión media y la reconversión, son 13.6±10.1 y 6.0±3.3 días respectivamente.

RESUMÉ

La présente communication est basée sur l'étude de 70 individus qui avaient viré spontanément leurs réactions tuberculiniques et qui reçurent de la prednisone au cours d'un traitement antituberculeux. Un test intradermique avec 50 unités de tuberculine fut pratiqué 72 heures avant, pendant et après l'administration de prednisone.

L'observation originale de Boquet et Bretey (1934)[18] selon laquelle il n'y a aucune corrélation entre l'intensité des réactions tuberculiniques et la sévérité de l'infection tuberculeuse se trouva confirmée.

Cette étude a montré qu'avec l'utilisation de prednisone en dosage convenable et pour une durée convenable, la sensibilité tuberculinique cutanée aussi bien dans les cas de tuberculoses actives que de tuberculoses inactives peut être totalement inhibée. Les taux moyens de conversion et de reconversion sont respectivement de 13,6±10,1 et 6,0±3,3 jours.

ZUSAMMENFASSUNG

Dem vorliegenden Bericht liegen 70 natürliche Tuberkulin-Konvertoren zugrunde, die im Verlauf einer antituberkulösen Behandlung Prednison erhielten. Intrakutane-Teste mit 5 Tuberkulineinheiten P.P.D. wurden in Abständen von 72 Stunden vor, während und nach einer Prednison-Behandlung vorgenommen.

Es wird die ursprüngliche Feststellung von Boquet und Bretey (1934)[18] bestätigt, wonach keine Korrelation besteht zwischen der Intensität zur Tuberkulinreaktion und der Schwere einer tuberkulösen Infektion.

Unsere Untersuchung hat ergeben, daß durch den Gebrauch mit Prednison in entsprechender Dosis und während eines angemessenen Zeitabschnittes die Kutane Tuberkulineempfindlichkeit sowohl bei aktiven sowie bei den inaktiven Fällen von Tuberkulose vollständig gehemmt sein kann. Die mittlere Reversions-und Rekonversionsrate liegt bei 13,6±10,1 und 6,0±3,3 Tagen.

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Infrapulmonary Pleural Effusion*

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The identification of pleural effusion on posterior-anterior and lateral chest roentgenograms is usually not difficult. However, when fluid collects between the lung and the diaphragm, assuming the contour of the diaphragm without obliterating or blunting the costophrenic sulcus, it can be deceptive in appearance and difficult to identify. Fluid localized between the diaphragm and the lung is known as infrapulmonary pleural effusion.

The reason for fluid collecting in this infrapulmonary distribution is not definitely understood. Friedman[1] suggests that as pleural fluid is formed it gravitates to the posterior and lateral costophrenic sulci, where capillary attraction draws it into the space between the visceral and parietal diaphragmatic pleura. In the majority of cases, as more fluid accumulates it will spill over and present the typical appearance of pleural effusion on the posterior–anterior chest roentgenograms (Fig. 1a and b). However, in some cases fluid will continue to maintain its position in the infrapulmonary position without spilling into the costophrenic sulci.

Infrapulmonary pleural effusion is not an uncommon condition. Although there are not many reports in the literature, the large number

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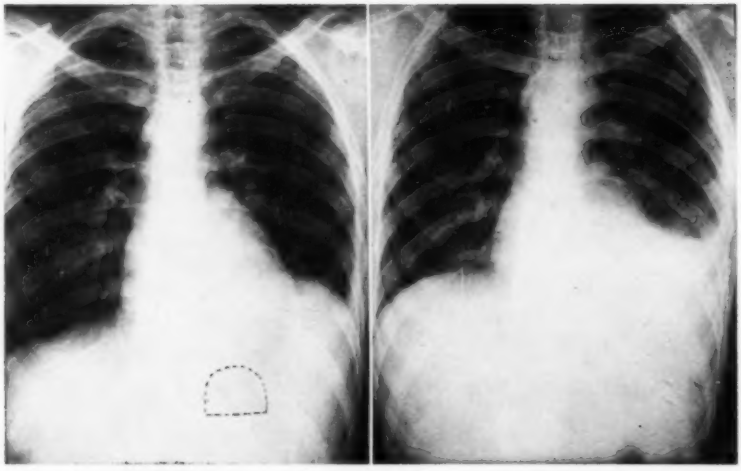

FIGURE 1a FIGURE 1b

FIGURE 1a: Infrapulmonary pleural effusion on the left side secondary to pneumonitis in the posterior basilar segment of left lower lobe. Note that the fluid assumes the contour of the left hemidiaphragm. The stomach bubble is outlined. FIGURE 1b: Twenty four hours later the fluid has spilled into the costophrenic sulcus and now has the typical appearance of pleural effusion ascending the lateral chest wall.

TABLE 1 — ETIOLOGY IN 19 CASES OF INFRAPULMONARY PLEURAL EFFUSION

Etiology	Number of Cases
Pneumonia	8
Thoracic Trauma	3
Idiopathic Effusion	2
Tuberculosis	1
Sarcoidosis	1
Cardiac Failure	2
Ruptured Spleen	1
Metastatic Malignancy	1
Total	19

of cases in most of the individual reports attest to its relative frequency of occurrence.[2-9]

In our own practice we have found that infrapulmonary pleural effusion is frequently encountered. We have often identified it in the postoperative period following thoracotomy. We have also observed it following thoracic and abdominal trauma and in various medical chest conditions. Excluding those patients who have had recent thoracotomies we have identified infrapulmonary pleural effusion in 19 cases in a 30-month period. Table 1 lists the types of cases in which we have encountered it.

When evaluating the posterior-anterior chest roentgenogram, infrapulmonary pleural effusion should be suspected whenever there is apparent elevation of the diaphragm. Infrapulmonary pleural effusion is more easily identified on the left side. On this side, there is not only the apparent elevation of the diaphragm but the presence of gas in the gastric bubble demonstrates an increased distance between the gastric bubble and the apparent elevated diaphragm. When the fluid is present on the right side, however, it is more difficult to detect because the

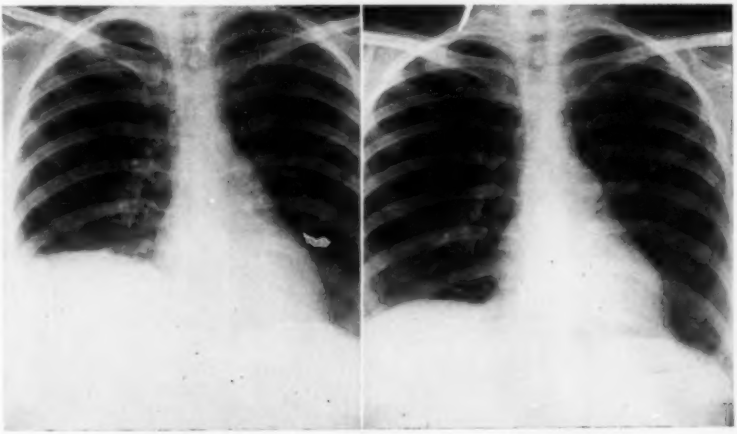

FIGURE 2a FIGURE 2b

FIGURE 2a: Chest roentgenogram shows an apparent elevation of the right hemidiaphragm. Because the surface was slightly irregular and the patient had chest pain, fluid was suspected. A lateral decubitus chest roentgenogram disclosed the presence of fluid. FIGURE 2b: Chest roentgenogram after thorcentesis with removal of 800 cubic centimeters of clear fluid.

density of the structures below the diaphragm is the same as fluid (Figs. 2a and b).

When an infrapulmonary pleural effusion is suspected, chest roentgenograms taken in the lateral decubitus position with the affected side down will usually demonstrate the presence of fluid. In this position the fluid will leave its infrapulmonary position and gravitate to the most dependent portion along the lateral costal margin (Figs. 3a and b).

Fluoroscopic examination of the chest may be of help in diagnosing suspected cases. The action of the heart may produce a wave-like motion on the surface of the fluid. Under fluorscopic control the fluid may be made to move from its infrapulmonary position to the lateral costophrenic sulcus by having the patient bend towards the affected side.

If the pleural effusion is on the left side, increasing the amount of gas in the gastric bubble may be of help in assessing the position of the diaphragm in doubtful cases. In suspected right-sided effusion, Friedman has used pneumoperitoneum to outline the under-surface of the diaphragm. We have not used this procedure.

In three of our cases the fluid assumed a contour suggesting an apparent lateral shift of the apex of the curve of what appeared to be the diaphragm (Fig. 4). This is an inconstant sign but when present it may be helpful in identifying infrapulmonary pleural effusion.

SUMMARY

Infrapulmonary pleural effusion should be suspected when either leaf of the diaphragm appears higher than normal. The presence of fluid is best confirmed on the lateral decubitus chest roentgenogram. The frequency with which infrapulmonary pleural effusion is identified appears to be dependent on the diligence with which it is sought. Nineteen cases of this condition have been reported and methods of identifying it have been discussed.

RESUMEN

El derrame infrapulmonar debe sospecharse cuando cualquiera de los hemidiafragmas parece más alto que lo normal. La presencia de líquido se confirma mejor en la radiografía de tórax en el decúbito lateral. La frecuencia con la cual se descubre el derrame infrapulmonar depende de la diligencia con que se busca. Se presentan en este trabajo 19 casos de esta posibilidad y se discuten los métodos para identificarla.

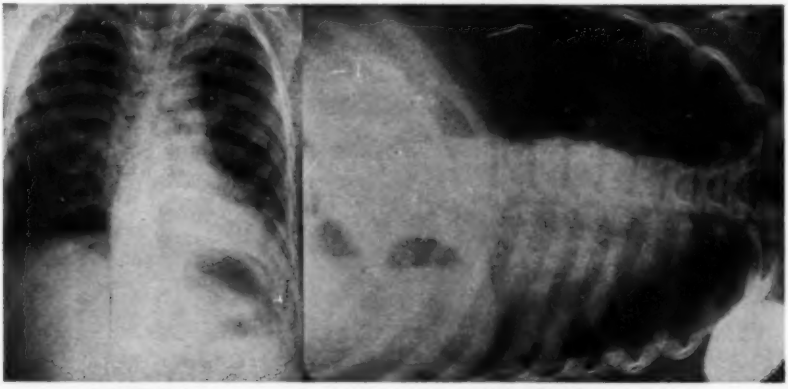

FIGURE 3a FIGURE 3b

FIGURE 3a: Infrapulmonary pleural effusion on the left side following abdominal trauma and rupture of the spleen. **FIGURE 3b**: Lateral decubitus examination of the chest demonstrates that the fluid is along the lateral chest wall.

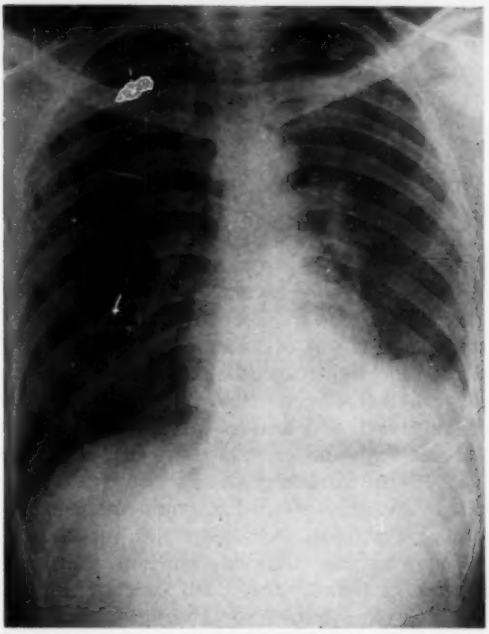

FIGURE 4: Chest roentgenogram shows tuberculosis involving the left upper lobe. There is an infrapulmonary effusion on the left. Note the lateral shift of the apex of the curve.

RESUMÉ

On devrait soupçonner un épanchement pleural infrapulmonaire quand l'un des feuillets diaphragmatiques semble plus élevé que la normale. La présence de liquide est mieux confirmée par la radiographie thoracique en décubitus latéral. La fréquence avec laquelle l'épanchement pleural infrapulmonaire est identifié semble dépendre de la diligence avec laquelle il est recherché. 19 cas de cet état ont été rapportés, et les méthodes d'identification sont discutées.

ZUSAMMENFASSUNG

An der Lungenunterfläche gelegene pleurale Ergüsse sollte man dann vermuten, wenn eine Zwerchfellkuppe höher steht als normal. Das Vorliegen von Flüssigkeit lässt sich am besten bestätigen bei Thoraxröntgenaufnahmen in Seitenlage. Die Häufigkeit, mit der ein pleuraler, unterhalf der Lunge gelegener Erguss identifiziert wird, scheint von der Sorgfalt abzuhängen, mit der danach gesucht wird. Über 19 Fälle dieser Art wird berichtet und Methoden diskutiert zu deren Erkennen.

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Current Concepts of Tuberculous Pleurisy with Effusion as Derived from Pleural Biopsy Studies

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It has long been accepted that pleurisy with effusion represents a manifestation of tuberculosis in 70-80 per cent of cases.[1,2] It has also been accepted until recent years that such effusion resulted from some type of allergic response of the pleura either to a subpleural tuberculous focus, or to the introduction of a relatively few tubercle bacilli into the pleural space, rather than from direct invasion of the pleura by tubercle bacilli. This concept grew out of Paterson's demonstration in 1917 of a marked pleural reaction in tuberculin sensitive guinea pigs when a few tubercle bacilli were introduced.[3] The older literature on this subject has been extensively reviewed and no attempt will be made to repeat this.[3,4] The "allergic" explanation has been employed more recently by Wallgren,[5] Miller,[6] Rich,[7] Lindskog and Liebow,[8] and Hinshaw and Garland.[9] However, the advent of pleural biopsy by aspiration or open thoracotomy techniques resulted in pathologic findings which cast doubt on the "allergic" theory as the total explanation. Thus, Sutliff,[10] Small,[11] Breckler,[12] Heller,[13] and Stead,[3] and their associates reported the presence of typical histologic evidence of tuberculosis of the pleura in from 70 to 100 per cent of cases studied by one or the other type of biopsy. The studies of Stead and his group[3] are of special interest in that all of their 24 cases underwent complete exploratory thoracotomy. Fifteen showed a chronic granulomatous pleuritis in 12 of which a caseous subpleural tuberculous focus could be demonstrated. Seven cases showed extensive small pulmonary foci which had not been demonstrable by x-ray. Donohue, Katz and Matthews[14] recently reviewed 111 patients on whom either needle or open thoracotomy biopsies, or both, were done. Granulomatous pleuritis was demonstrable in about 70 per cent of cases whose clinical courses warranted a diagnosis of tuberculosis. Strauss, Loring, and Henderson[15] reported on pleural biopsy studies on 200 patients with pleural effusion both tuberculous and non-tuberculous. The tuberculous cases showed five histologic patterns: "(1) acute, edematous, hypercellular pleura, (2) non-caseating granulomata, (3) classical caseating tubercles, (4) confluent caseation with associated fibrosis, hyalinization, and calcification, and (5) hyalinized and fibrous whorls of tissue." They state: "In pleural tuberculosis the pleura is diffusely involved by the characteristic spectrum of tuberculosis and there is little to support the former concept that tuberculous pleural effusions are due to allergic phenomenon."

Between 1953 and 1958, 28 pleural biopsies were done at the Veterans Administration Hospital in East Orange, N. J. Of these, 21 were ultimately diagnosed as tuberculous on the basis of the biopsy reports, clinical course, response to therapy, the presence of tuberculosis elsewhere, skin test conversion, and, unusually, the identification of tubercle bacilli.

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These 21 cases form the basis of this report. The procedure used was the limited open thoracotomy as described by Small and Landman.[11] The period of time between the onset of pleural effusion and biopsy ranged from one to nine months (average 4½ months). No correlation could be established between the mode of onset, length of delay before surgery, or the prior use of anti-tuberculous chemotherapy, and the subsequent pathologic findings. Postoperative complications were seen in only two patients. The most serious was the development of a bronchopleural fistula which necessitated further chest surgery. A transient subcutaneous and mediastinal pneumothorax was the other complication noted. Twenty two of the total group were ambulatory the day after the operation. In all cases the gross observations at surgery revealed an apparently diffuse process.

The histological reports could readily be classified into four types: (1) Tuberculosis of the pleura with caseous necrosis: six cases; (2) epithelioid giant cell granulomata of the pleura, compatible with tuberculosis: five cases; (3) acute fibrinous pleurisy, non-specific: three cases; and (4) fibrous thickening of the pleura: seven cases. Thus, our findings tend to support the belief that in the majority of cases of tuberculous pleurisy with effusion, there is extensive involvement of the pleura by the tuberculous process. This concept explains the frequency with which pleural involvement in this disease is associated with chest wall abscesses, Pott's Disease and generalized spread — the infected pleura providing a large area for lymphatic contamination.

The following representative cases will illustrate the basic findings plus certain other interesting observations:

CASE 1: Mr. HSD was a 40 year old Negro who had a diagnosis of left idiopathic pleurisy with effusion in October, 1954, treated with bed rest and penicillin. In June, 1955, he developed right pleurisy with effusion. A needle biopsy done July 8th was reported to show only "fibrous thickening," but pleura obtained by open thoracotomy (Figure 1) showed the typical histologic picture of tuberculosis.

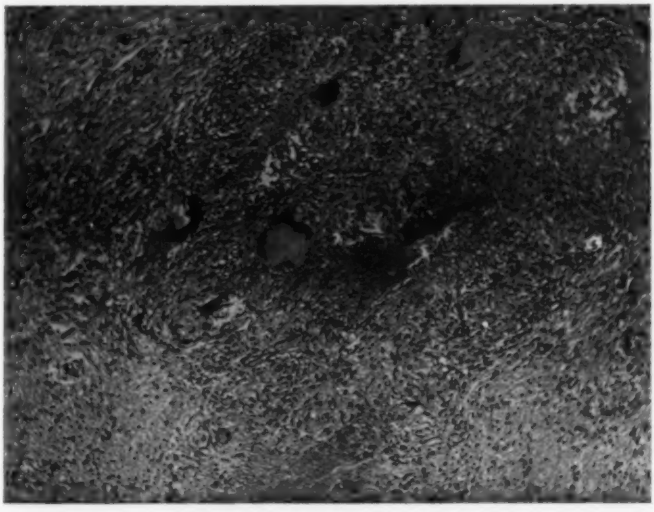

FIGURE 1 — (case 1): Typical epithelioid giant cell tubercle with caseous necrosis. This is characteristic of the histologic findings in 6 cases.

CASE 2: Mr. WGK was a 32 year old white man who had a presumptive diagnosis of tuberculous pleurisy because of typical clinical features and a close family contact. However, a cell block made from aspirated pleural fluid was reported to be "highly suspicious of lymphoma." Pleural biopsy by open thoracotomy was done and a diagnosis of tuberculosis was established on the basis of typical histologic findings similar to the first case. Antituberculous chemotherapy effected complete clearing.

CASE 3: Mr. AHJ was a 43 year old Negro who sought admission for an anxiety reaction but the chest x-ray film showed massive left pleural effusion. Pleural biopsy, done 10 days after the clinical onset, revealed the tissue changes pathognomonic of tuberculosis, as in the first two cases. Streptomycin and para-aminosalicylic acid were started. There was prompt clearing of the pleural process, but six months after discharge and after 18 months of therapy, he was readmitted with the findings of chronic hematogenous pulmonary tuberculosis.

CASE 4: Mr. JWH was a 28 year old Negro, of alcoholic habits, whose symptomatology began in April, 1954. When admitted in October, the x-ray film showed pleural effusion. Biopsy done one month later showed caseous pleural tuberculosis. Despite treatment with streptomycin and para-aminosalicylic acid, started early in November, an x-ray film in December showed evidence of miliary spread. He left the hospital against medical advice in January but returned one month later with tuberculous meningitis.

CASE 5: Mr. IB was a 62 year old white man who had episodes of active pulmonary tuberculosis in 1922, 1929, and 1939. In July, 1957 the clinical and x-ray findings of left pleural effusion developed. Because of his age, the possibility of neoplasm was considered but pleural biopsy showed "epithelioid giant cell granulomata consistent with tuberculosis" (Figure 2). Later, two positive sputum cultures were reported. This case is presented not only to demonstrate this type of pathology, but to show an exception to the adage that tuberculous pleurisy occurs in young people in the post primary state.

CASE 6: Mr. WMT was a 28 year old Negro whose clinical course and chest x-ray films were similar to the others but whose pleural biopsy (Figure 3) done two months after the onset, showed only an "acute non-specific fibrinous pleuritis." One month later distress in his right leg developed and x-ray films considered characteristic of tuberculosis of the knee joint, fibula and tarsal joints were obtained. Both the bone and chest findings cleared promptly on triple drug therapy. This case represents a "false negative" and is an example of the third type of tissue response.

CASE 7: Mr. PLO was a 33 year old white man who presented with cough, anorexia, weight loss, night sweats and right pleuritic — type chest pain for four months, x-ray film showed evidence of effusion. Pleural biopsy (Figure 4) recovered only pleura thickened by granulation tissue. This is typical of the non-specific pleural fibrosis found in both tuberculous and non-tuberculous cases. However, a biopsy of an acneiform rash of the face found typical epithelioid giant cell tubercles. This case again emphasizes that the failure to recover diagnostic tissue by pleural biopsy does not exclude tuberculosis. In the recent review by Dr. Katz's group,[23] it was noted that

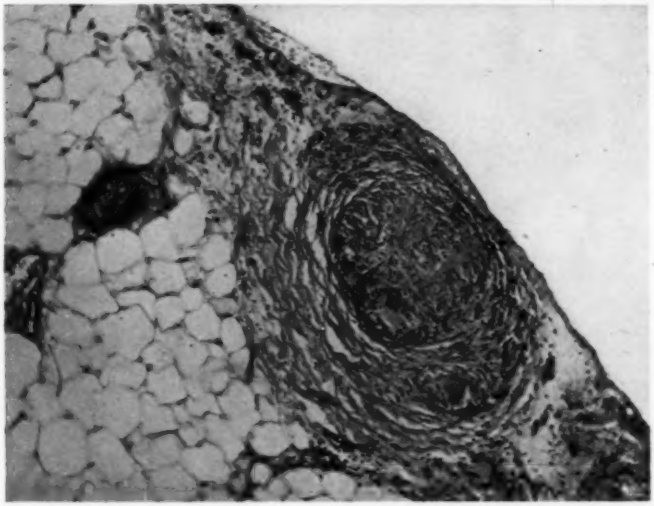

FIGURE 2 — (case 5): Epithelioid giant cell granuloma of the pleura, typical of the findings in 7 cases.

false negatives were equally frequent in biopsies taken by the needle method and limited thoracotomy, but not when complete exploration was carried out.

To maintain perspective, attention should be called to the other causes of pleural effusion. The list would include malignancy, pneumonia, chronic lung abscess, rheumatic fever, nephrotic syndrome, cirrhosis of the liver, infectious mononucleosis, congestive heart failure, pulmonary embolism, collagen-vascular diseases, and the pleural component of idiopathic pericarditis. Of these, only the first, malignancy, is likely to be associated with specific tissue changes.

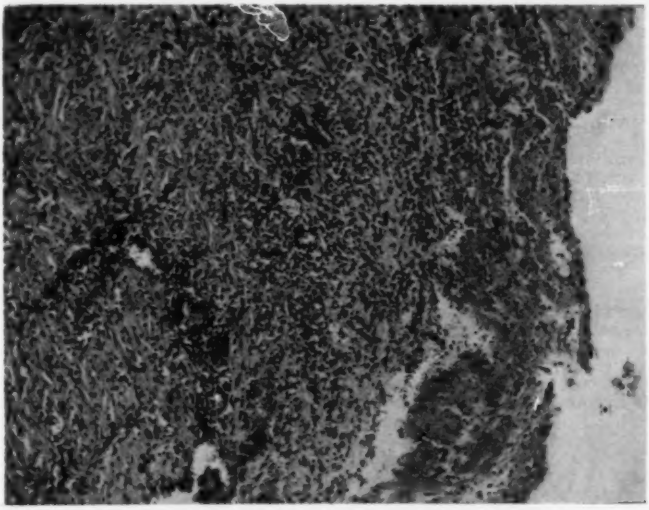

FIGURE 3 (case 6): Acute fibrinous pleurisy as noted in 3 cases. This type of histologic change is non-specific.

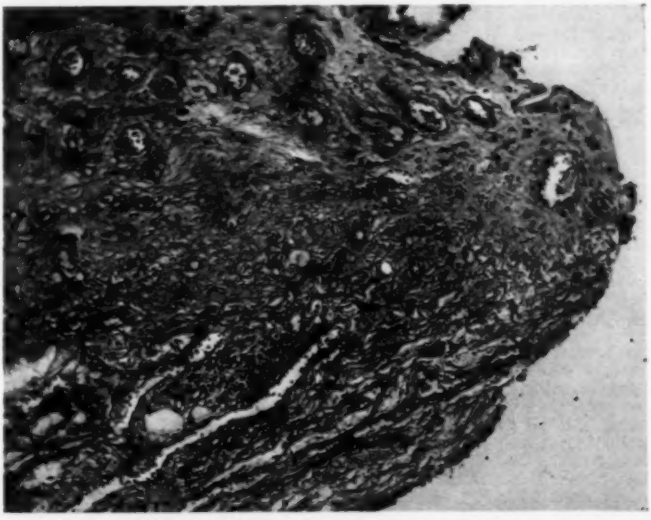

FIGURE 4 (case 7): Fibrous thickening of the pleura; a finding noted in 7 cases. This was also the most frequent pathologic diagnosis in cases of non-tuberculous pleurisy.

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SUMMARY

Eleven of 21 patients with the clinical diagnosis of tuberculous pleurisy with effusion showed pleural tissue changes at biopsy characteristic of this disease. It is to be emphasized that these were selected cases in that a diagnostic problem existed at the time of operation. Furthermore, only a 1.5 by 3 cm. piece of parietal pleura was obtained by the operative method used and only a small area was directly observed. The extent and character of the pleural involvement was impressive when considered in relation to prior concepts.

In view of our findings, plus those reported in the recent literature, the natural history of tuberculous pleurisy with effusion might be conceived as beginning with the rupture of a subpleural caseous focus into the pleural space. This occurs frequently, but by no means always, in the post-primary phase. The hypersensitive pleura may or may not respond with the outpouring of an effusion at this time, but in any event, there is extensive invasion of the pleura by the tubercle bacilli leading to sufficient inflammation to produce the large amount of fluid often observed in this entity. The disease may then resolve completely in from 30 — 60 per cent of cases, lead to invasion of the chest wall, spine, lungs, or blood stream in perhaps 5 per cent of cases, or temporarily resolve and recur within five years in one or both lungs in about 23 per cent, (2) but perhaps as much as 65 per cent (4) of cases. Pleural biopsy, properly done by any method, helps to establish the diagnosis of this potentially grave disease and, equally important, helps to avoid unnecessary treatment and stigma in others.

RESUMEN

De 21 enfermos con el diagnóstico clínico de pleuresía tuberculosa con derrame, 11 mostraron cambios tisulares característicos de esta enfermedad en la biopsia. Debe hacerse notar que se trataba de casos escogidos en los que existía un problema de diagnóstico al tiempo de la operación. Más aún, se obtuvo solamente piezas de pleura parietal de 1.5 por 3 cms. por el método operatorio y sólo una área pequeña fué observada directamente. La extensión y el carácter del compromiso pleural, fué impresionante en relación con los conceptos anteriores.

En vista de nuestros hallazgos, además de los relatados en la literatura, la historia natural de la pleuresía tuberculosa con derrame podría concebirse como que empieza con la ruptura de un foco subpleural caseoso hacia el espacio pleural. Esto ocurre más frecuentemente, pero no siempre en el estado post-primario.

La pleura hipersensible puede responder o no por el derrame en esa ocasión, pero en todo caso hay una invasión extensa de la pleura por el bacilo tuberculoso que conduce a una inflamación suficiente para producir una gran cantidad de líquido en esta afección. La enfermedad puede resolverse favorablemente en 30 a 60 por ciento de los casos; o conducir a invasión de la pared torácica, de la columna vertebral, de los pulmones o invadir la corriente sanguínea probablemente en 5 por ciento de los casos o bien resolverse temporalmente y recurrir dentro de 5 años en uno o ambos pulmones aproximadamente en 23 por ciento (2) pero probablemente hasta en 65 por ciento (4) de los casos.

La biopsia pleural llevada a cabo adecuadamente por cualquier método ayuda a establecer el diagnóstico de esta enfermedad potencialmente grave, igualmente importante, y ayuda a evitar el tratamiento innecesario y el estigma en otros.

RESUMÉ

Parmi 21 malades pour lesquels on avait porté le diagnostic clinique de pleurésie tuberculeuse avec épanchement, onze montrèrent à la biopsie des altérations du tissu pleural caractéristiques de cette affection. Il faut insister sur le fait que ces cas avaient été choisis parce qu'ils posaient un problème de diagnostic. De plus, on n'obtint qu'un fragment de plèvre pariétale de 1,5 à 3 cm. par la méthode opératoire utilisée, et seule une petite zone fut directement observée. L'étendue et le caractère de l'atteinte pleurale furent impressionnants si on les considèrent par rapport aux conceptions antérieures.

Selon nos constatations, et celles rapportées dans la littérature récente, l'histoire de la pleurésie tuberculeuse avec épanchement pourrait être conçue comme commençant par la rupture dans l'espace pleural d'un foyer caséeux souspleural. Cette situation se présente souvent, mais non pas d'une façon constante au cours de la phase post-primaire. La plèvre hypersensible peut ou non répondre par le déclenchement d'un épanchement à ce moment, mais dans tous les cas, il y a une invasion extensive de la plèvre par les bacilles tuberculeux amenant une inflammation suffisante pour produire la grande quantité de liquide souvent observée. L'affection peut alors guérir complètement dans 30 à 60% des cas, amener l'invasion de la paroi thoracique, de la colonne vertébrale, des poumons, ou de la circulation sanguine dans petu-être 5% des cas, ou se résorber momentanément, et réapparaitre dans un délai de cinq ans dans un poumon ou les deux dans environ 23% mais pouvant peut-être atteindre 65%

des cas. La biopsie pleurale, correctement faite par toute méthode, permet d'établir le diagnostic de cette affection potentiellement grave, et -point important également — permet d'éviter un traitement inutile dans d'autres cas.

ZUSAMMENFASSUNGEN

Bei 11 von 21 Kranken mit der klinischen Diagnose einer tuberkulösen Pleuritis mit Erguss zeigten sich pleurale Gewebsveränderungen bei der Biopsie, die für diese Krankheit kennzeichnend ist. Es muss hervorgehoben werden, dass es sich dabei um ausgewählte Fälle handelte, bei denen zum Zeitpunkt der Operation die Diagnose noch nicht sicher feststand. Ferner ermöglichte die operative Methode nur, ein Gewebsstückchen der Pleura in der Grösse von 1,5:3cm zu gewinnen, und es wurde nur ein kleiner Bereich direkt beobachtet. Die Ausdehnung und der Charakter der pleuralen Beteiligung waren eindrucksvoll bei der Erwägung im Vergleich zu früheren Auffassungen.

Im Hinblick auf unsere Befunde, sowie au-f die in der jüngsten Literatur mitgeteilten Beobachtungen, kann man die Entwicklungsgeschichte der tuberkulösen Pleuritis mit Erguss so auffassen, dass sie mit der Ruptur einer subpleuralen Käseherdes in den Pleuraspalt hinein beginnt. Dies geschieht häufig, jedoch keineswegs immer während der postprimären Phase. Die überempfindliche Pleura kann zu diesem Zeitpunkt mit der Bildung einer Ergusses reagieren, oder sie tut es auch nicht; in jedem Fall aber kommt es zu einer intensiven Invasion der Pleura durch den Tuberkelbazillus, und dies führt zu einer so beträchtlichen Entzündung, dass die grossen-oft bei diesem Leiden beobachteten-Flüssigkeitsmengen entstehen. Die Erkrankung kann sich in 30 — 60% der Fälle vollständig zurückbilden, kann zu einer Beteiligung der Brustwand führen, bezw. der Wirbelsäule, der Lungen oder des strömenden Blutes in vielleicht 5% der Fälle oder sich vorübergehend zurückbilden und innerhalb von 5 Jahren in einer oder beiden Lungen in ungefähr 23% wieder auftreten (2), aber vielleicht auch in nicht weniger als 65% der Fälle (4). Die Biopsie der Pleura dient, wenn sie sorgfältig nach irgendeiner Methode durchgeführt wird, zur Sicherstellung der Diagnose dieser potentiell ersten Erkrankung und trägt, was gleichfalls wichtig ist, dazu bei, in anderen Fällen eine unnötige Behandlung und Brandmarkung zu vermeiden.

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The Effect of Xanthin Derivatives: Ro 1-8239, Aminophylline and Dihydroxy Theophylline on Chronic Pulmonary Disease*

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Introduction

The widespread use of various xanthine derivates in chronic pulmonary disease have prompted numerous studies on the action of these drugs in both pulmonary function and cardiocirculatory system.

It has been shown that aminophylline and dihydroxytheophylline (DHT) have bronchodilator properties[1,2] increasing ventilation by direct stimulation of the respiratory center.[1]

The object of the present study is to test the effect of various xanthinic compounds on the respiratory function of patients with chronic pulmonary disease, especially of the new compound Ro 1-8239 (X-D).**

Material and Methods

This study comprises 23 patients, of whom five had advanced, seven had moderately advanced pulmonary emphysema and 11 emphysema with various degrees of pulmonary fibrosis. These patients were studied on 35 different occasions at rest and 30 minutes after intravenous administration of aminophylline 0.25 gm (seven studies); DHT 0.25 gm (eight studies) and X-D 0.10 gm (20 studies). The observations included complete spirometric studies, determination of arterial blood O_2, CO_2, pH, CO_2 tension, blood hemoglobin O_2 capacity, expiratory minute volume, alveolar ventilation, tidal volume, frequency of respiration, physiological dead space and physiological dead space/tidal volume ratio. All observations were made according to accepted methods and have been described elsewhere.[3] Three normals and five patients with tight mitral stenosis served as controls.

Results

No significant difference was found between the action of aminophylline, DHT and X-D in the spirometric studies or in any of the parameters determined. No statistically significant effect was produced on vital capacity. expiratory reserve, inspiratory capacity, maximum minute volume 30 minutes after intravenous administration of any of the tried drugs. In 11 patients at least two drugs were tried on different occasions. Table I shows the action of X-D on the 20 cases studied with this drug.

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*From the Instituto de Cirugia Cardiovascular y del Torax.
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**Supplied by Hoffman La Roche.

Discussion

The degree of significant reduction in physiological dead space, without changes in tidal volume known to affect it, is of practical importance. This reduction may be due to: 1. An increased ventilation in areas which were well perfused and poorly or non-ventilated, 2. An increase perfusion in areas which were well ventilated and poorly or non-perfused, or 3. Both. The absence of changes in maximum minute volume and vital capacity, as well as the behaviour of respiratory minute volume and tidal volume, suggest, that bronchodilatation is not an important factor. Consequently, it appears more likely that the main effect of X-D is through an improvement in capillary circulation. Local pulmonary vasodilatation with xanthinic compounds have recently been demonstrated in perfused lungs.[6]

TABLE I

	t	p	Difference between means	Mean effect
Physiological dead space (ml)	3.26	0.01	27.5	decrease
V_D/V_T	3.33	0.01	4.8	decrease
Alveolar ventilation (L/min.)	3.14	0.01	0.44	increase
Arterial pCO_2 (mm Hg)	3.42	0.01	2.43	decrease
Arterial pH (units)	3.00	0.01	0.028	increase
Arterial O_2 saturation (per cent)	4.02	0.01	3.7	decrease
Arterial O_2 content (vol per cent)	2.15	0.05	0.27	decrease
O_2 capacity (vol per cent)	2.43	0.05	0.56	increase
V (L/min)	1.32		0.26	decrease
V_T (ml)	1.37		10.8	decrease
f	0.30		0.06	decrease

Anatomical dead space was not determined in these studies, but it seems safe to assume that it remained unchanged or possibly increased, since xanthines are known bronchodilators. Alveolar dead space represents the difference between physiological and anatomical dead space. Consequently, a significant reduction in alveolar dead space is implicity included in the reduction of physiological dead space. Severinghaus and Stupfel[4] have shown that alveolar dead space (expressed as a percentage of alveolar tidal volume) is roughly equal to the percentage of non-perfused lung. Thus, a reduction in alveolar dead space means an increase in perfusion. Overventilation of alveoli which would produce the same effect appears unlikely. A reduction of V_D/V_T ratio is interpreted in the same manner.[5]

The significant increase in alveolar ventilation is a corollary to the reduction in the physiological dead space. It determines the reduction in pCO_2 and this leads to an increase in pH.

The absence of a statistically significant reduction in CO_2 content of arterial blood is in agreement with the findings of Moyer et al[6] and may be explained by the shape and position of the physiological dissociation curve of CO_2, which permits easier measurements of changes in tension with minimal changes in CO_2 content.

The small but significant reduction in arterial blood oxygen saturation is explained as variations in the ventilation-perfusion ratios throughout the lung.[7] Furthermore, personal observation on some of these patients during catheterization, as well as those of Quimby[8] suggest that since the drug acts on both pressure and cardiac output, its effect may increase the flow through pulmonary A-V shunts and produce unsaturation. It is somewhat surprising that no significant increase in pulmonary ventilation was observed, as one would anticipate if the various xanthinic compounds have a stimulatory action on the respiratory center. The results agree with the findings of Richmond.[9] It is difficult to attempt an evaluation of a stimulant action on the respiratory center by injection of a drug, particularly in patients with increased pCO_2. Both lowering of pCO_2 and an increase in pH tend to inhibit the respiratory center, and both these actions are obviously peripheral effects of the drug. Secondly the lack of uniform hyperventilation may be due to the small dose employed.

Recent observations on patients with Cheyne-Stokes type of respiration[10] where xanthine compounds have been more widely used, seem to indicate that there are two types, as revealed by the behaviour of lung compliance, a central and a peripheral type. It can be anticipated that the peripheral type would be the most likely to be corrected using the dose employed in the present study.

SUMMARY

There is no significant difference between the action of aminophylline, dihydroxytheophylline and xanthin derivative Ro 1-8239 on chronic pulmonary disease.

Intravenous injection of various xanthinic compounds produce an important signifi-

cant reduction of physiological dead space and V_D/V_T ratio, an increase in alveolar ventilation, decrease in pCO_2, arterial oxygen saturation and an increase in arterial pH. These actions are best explained as an improvement in the ventillation-perfusion ratio, with or without bronchodilatation.

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RESUMEN

No hay diferencia significativa entre la acción de la aminofilina, la dihidroxiteofilina y el derivado de la xantina Ro.-1-8239 en la enfermedad pulmonar crónica.

La inyección intravenosa de varios compuestos xantínicos produce una reducción significantiva del espacio muerto fisiológico y la relación V_D/V_T; un aumento de la ventilación alveolar, disminución de pCO_2, saturación arterial de oxígeno y un aumento de pH arterial. Estas acciones son explicadas mejor como una mejoría de la relación ventilación-perfusión con o sin broncodilatación.

RESUMÉ

Il n'y a pas de différence significative entre l'action de l'aminophylline, de la dihydrothéophylline, et des dérivés xanthiniques Ro 1-8239 sur la maladie pulmonaire chronique.

L'injection intraveineuse de différents composés xanthiniques produit une diminution nette de l'espaces mort physiologique, un accroissement de la ventilation alvéolaire, une diminution de la teneur en gaz carbonique, une saturation artérielle oxygénée, et une augmentation du pH artériel. Ces actions sont mieux expliquées si l'on fait appel à l'amélioration du quotient ventilation-perfusion, avec ou sans bronchodilatation.

ZUSAMMENFASSUNG

Es besteht kein entscheidender Unterschied zwischen der Wirkung von Aminophyllin, Dihydroxythelphyllin und dem Xanthin-Abkömmling Ro 1-8239 bei chronischer Lungenkrankheit.

Die intravenöse Injektion verschiedener xanthinhaltiger Verbindungen bewirkt eine wesentliche Verringerung ds physiologischen Todraumes, einen Anstieg der alveolären Belüftung, eine Abnahme des pCO_2, der arteriellen Sauerstoffsättigung und eine Zunahme des arteriellen pH. Diese Einflüsse lassen sich am besten erklären als eine Verbesserung des Verhältnisses von Ventilation zur Durchströmung mit oder ohne Erweiterung der Bronchien.

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A Study of Gastric Secretions in Chronic Obstructive Pulmonary Emphysema

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In a previous communication,[1] we demonstrated that the incidence of chronic peptic ulceration in patients with chronic obstructive pulmonary emphysema is greater than would be expected by chance alone. Since a relationship between gastric acidity and arterial carbon dioxide tension might be postulated, a study of gastric secretions in this disease entity was done.

Materials and Method

Thirty unselected subjects with chronic obstructive pulmonary emphysema were studied. The diagnosis in each instance was substantiated by fluoroscopic observation and evaluation of pulmonary function.

Each patient was studied in the fasting state. Intubation was carried out under fluoroscopic control and an indwelling arterial needle was inserted. Continuous gastric suction was applied until successive pH determinations agreed by 0.5 pH units. This usually consumed 50 to 70 minutes. pH was determined with a Cambridge Model R pH meter. Free acidity was determined by titration.[2] Coincident with the final "basal" gastric juice collection, an arterial blood specimen was collected. Arterial oxygen saturation, carbon dioxide content and tension, and pH were determined by standard techniques.[3-5]

Twenty-one of these subjects were then given carbon dioxide inhalations for 30 minutes each. Seven of these received 95 per cent oxygen and 5 per cent carbon dioxide and 14 inhaled 5 per cent carbon dioxide in air. Samplings of gastric juice and arterial blood were carried out during this period and for an ensuing 30 minutes.

Control subjects consisted of 10 patients, over 40 years of age, who had no pulmonary or gastrointestinal disease. They were intubated and

	No.	Mean	S.D.	Probability	95 % Conf. Limits
pH					
Control	10	4.465	2.54	.002 < P < .005	2.19 to 2.45
Pul. Emphysema	30	2.144	1.52		
Free Hcl					
Control	10	15.60	27.93	.02 < P < .05	8.78 to 38.66
Pul. Emphysema	30	35.37	24.84		

TABLE 1

From the Medical Service, Veterans Administration Hospital and Department of Medicine, University of Miami School of Medicine.

gastric juice continuously sampled until the pH of successive aspirations agreed within 0.5 pH units.

Results

A summation of the values for gastric juice pH and free acidity in the 30 pulmonary emphysema patients and the 10 controls is given in Table 1. The mean gastric juice pH for the pulmonary emphysema group was 2.14, while that for the control group was 4.47. The difference between these means was statistically significant. The mean gastric juice free HC1 for the emphysema patients was 35.4 units, while the mean value for the controls was 15.6. The difference between these means was also statistically significant.

The results of the arterial blood determinations were analyzed in relation to gastric acidity and pH. There were no significant linear correlations between gastric juice, free HC1 and the arterial pH, CO_2 tension or arterial oxygen saturation. The pH of the gastric juice similarly did not exhibit any correlations with the arterial blood determinations. Figs. 1 and 2 are scattergrams obtained by plotting gastric juice pH against arterial CO_2 tension (pCO_2) and gastric free HCL against arterial CO_2 tension (pCO_2) and gastric free HCl against arterial pH, illustrating this poor correlation.

Preliminary studies in eight subjects with chronic pulmonary emphysema had revealed a negligible effect of gastric suction for 50 to 90 minutes on the arterial blood measurements.

During the carbon dioxide inhalation period in 21 subjects there were no consistent or significant alterations in gastric juice pH or free HCl; thus, the mean change with inhalation of 5 per cent carbon dioxide in

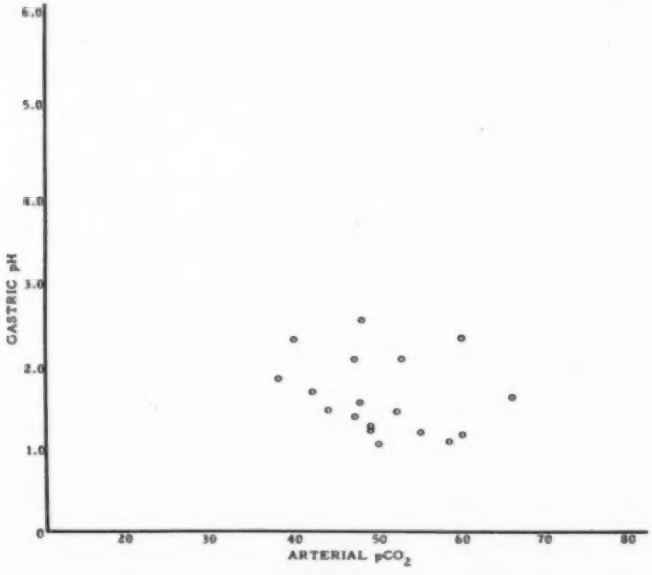

FIGURE 1

oxygen in seven subjects was +0.50 pH units and +15 free HCl units, while after inhalation of 5 per cent carbon dioxide in air the mean alteration in 14 subjects was +0.16 pH units and −1.3 free HCl units.

Comment

Significantly increased gastric acidity in this group of fasting pulmonary emphysema patients has been demonstrated. The hypothesis that carbon dioxide retention is implicated in this phenomenon could not be substantiated in this series. The carbonic anhydrase theory of gastric hydrochloric acid secretion[6] visualized rapid hydration of endogenous carbon dioxide in the parietal cells of the gastric mucosa. Ionization of the carbonic acid was seen to give rise to the hydrogen ions of the parietal secretion. It is of interest that Davenport[7] in 1946 retracted his theory when it was shown that carbonic anhydrase inhibitors do not inhibit secretion of hydrochloric acid except when present in large quantities.

It might also be postulated that stress is a common denominator in both chronic peptic ulcer and chronic pulmonary emphysema. There is some indirect evidence favoring the hypothesis that gastric and adrenal activity are closely related. It is well known that peptic ulceration is exceedingly rare in Addison's disease. On the other hand, the administration of cortisone has been followed by gastric and duodenal ulceration in Addison's disease.[8-9] It is also well known that the administration of adrenal glucocorticoids has resulted in the development of epigastric pain or peptic ulcer in patients without previous gastrointestinal disease, and has led to the reactivation of quiescent peptic ulceration.

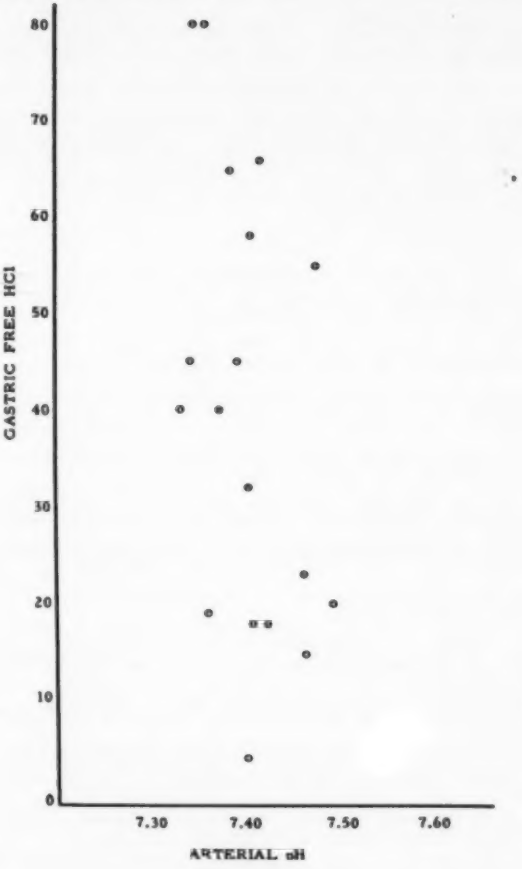

FIGURE 2

Studies in human subjects have indicated a marked increase in gastric acid and pepsin secretion after administration of corticotropin.[10] It has been suggested that in the basal state the stomach acts semi-autonomously relative to the adrenal cortex.[11] However, Weed and his co-workers found normal plasma corticosterone and cortisol levels in 10 patients with peptic ulcers.[12]

Further studies relating to adrenal cortical activity in patients with pulmonary emphysema and in patients with pulmonary emphysema and peptic ulcer appear to be indicated.

SUMMARY

Significantly increased gastric juice, free acidity and decreased gastric pH were demonstrated in 30 unselected patients with chronic obstructive pulmonary emphysema. There was no evidence supporting the hypothesis that carbon dioxide retention may be a factor. A possible stress mechanism was discussed.

RESUMEN

En 30 enfermos no seleccionados, de enfisema pulmonar crónico obstructivo se encontró un aumento del jugo gástrico, de la acidez libre y decrecimiento del pH. No hay evidencias de que pueda ser un factor la retención de bióxido de carbono. Se diserta sobre la posibilidad de un mecanismo de stress.

RESUMÈ

Une nette augmentation du suc gastrique, une franche acidité et une diminution du pH gastriques furent mis en évidence chez 30 malades choisis au hasard et atteints d'emphysème pulmonaire obstructif chronique. Aucun argument ne permet d'envisager l'hypothèse selon laquelle la rétention de gaz carbonique puisse être le facteur causal. La possibilité d'un mécanisme de stress est discutée per les auteurs.

ZUSAMMENFASSUNG

Ein beträchtlich vermehrter Magensaft, erhöhte freie Säure und herabgesetzte Magen-pH-Werte wurden nachgewiesen bei 30 nicht ausgesuchten Kranken mit chronischem obstruktivem Lungenemphysem. Ez ergab sich kein Anhalt der die Hypothese unterstützt hätte, wonach eine CO_2— Retension ein Faktor für das Zustandekommen dieser Erscheinungen wäre. Dieskussion eines möglichen Stress-Mechanismus.

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SECTION ON CARDIOVASCULAR DISEASES

Group A beta Hemolytic Streptococci and Rheumatic Fever in Miami, Florida:

III. Bacteriologic Observations on beta Hemolytic Streptococci Other Than Group A.

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The Lancefield groups of beta hemolytic streptococci other than group A have received relatively little consideration from investigators of the bacteriological flora of the human throat, probably because non-group A organisms were considered infrequent human invaders. In our studies of beta hemolytic streptococci in children attending the first three grades of the public schools in the Greater Miami (Dade County) area, groups B, C, F and G have been recovered from throat cultures sufficiently often to impel us to comment here on their frequency. The frequency of recovery of group A beta hemolytic streptococci in the same children has been reported in earlier communications.[1-5]

Methods and Material

Baseline Studies:—From February to June, 1953 (pilot study[1]), and from October, 1953 to June, 1954 (second study[2]), and from October, 1954 to June, 1955 (third study[3]), duplicate throat swabs were taken from children attending the first three grades in the public schools of Dade County, Florida, as previously described.[1-5] The pairs of throat swabs were streaked on culture plates as soon as possible, always within two hours of collection. One swab was streaked onto a plate containing blood agar base (Difco), and the other swab onto a plate of neopeptone heart infusion agar. Each of the two media had been enriched with 4 per cent defibrinated sheep's blood. After 24 hours' incubation at 37°C, plates were read for beta hemolysis. Pure cultures were isolated and sent to Dr. Elaine Updyke, Communicable Disease Center, Chamblee, Georgia for Lancefield grouping and typing.

Venous blood was drawn aseptically on many children in the second and third periods of the study, at the same time throat cultures were taken. These blood samples were allowed to clot, and the sera drawn off. All sera were stored in a deep freeze until the June following the

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drawing of the bloods, at which time antistreptolysin O (ASLO) determinations were made, using commercial (Difco) streptomycin O reagent.

During the third study period (October, 1954 - May, 1955) closer correlation between the presence of streptococci in the throat and serological responses to these organisms was sought. Whenever a beta hemolytic streptococcus was recovered, follow-up throat cultures and blood samples were obtained 2, 4 8 and 16 weeks later. If a child was absent from school at the time sampling was scheduled, every attempt was made to get a culture within 72 hours, either at the child's home or at school, if he returned.

County-wide Studies:—In addition to these studies during the third study period, a county-wide study was carried out at 48 additional schools. Six different schools were visited each month during the school year of October, 1954 - May, 1955, (December was omitted because of the long Christmas vacation). At each of these schools, 25 children from the first, second, and third grades had their throats swabbed one time only. Thus, a total of 1200 additional cultures comprise this section of the investigation.

Studies of Different Age Groups:—During a fourth period of study, October, 1955 through May, 1956, the investigation involved four different groups; (1) Each month 100 children (25 in each of 4 different schools) attending the first three grades had throats swabbed once only. A total

TABLE 1—BETA HEMOLYTIC STREPTOCOCCI, EXCLUSIVE OF GROUP A, ISOLATED FROM 11,014 THROAT CULTURES, FEBRUARY 1953-MAY 1956, MIAMI, FLORIDA

	Cultures Examined	B	C	F	G	NG†	Total	Total Per cent
Baseline Studies:								
Feb.-May, 1953 (A*)	1154	6	4	0	1	2	13	1.1
Oct. 1953-May '54 (B*)	2809	28	37	3	30	2	100	3.6
Oct. 1954-May '55 (E*)	2437	31	126	34	75	1	267	11.0
Totals	6400	65	167	37	106	5	380	5.9
Per cent	—	1.0	2.6	0.6	1.7	0.1	5.9	—
County-wide Studies:								
Oct. 1954-June '55 (E*)	1200	16	34	13	42	0	105	8.8
Oct. 1955-May '56 (E*)	798	8	36	9	36	15	104	13.0
Oct. 1955-May '56 (J*)	801	6	21	4	46	17	94	11.6
Totals	2799	30	91	26	124	32	303	10.8
Per cent	—	1.1	3.2	0.9	4.4	1.1	10.8	—
Totals for Children	9199	95	258	63	230	37	683	7.4
Per cent	—	1.0	2.8	0.7	2.5	0.4	7.4	—
Adult Studies:								
Oct. 1955-May '56 (R*)	800	19	13	5	9	13	59	7.4
Oct. 1955-May '56 (NR*)	1015	30	21	9	15	25	100	9.9
Totals for Adults	1815	49	34	14	24	38	159	8.8
Per cent	—	2.7	1.9	0.8	1.3	2.1	8.8	—
Grand Totals	11014	144	292	77	254	75	842	7.6
Per cent	—	1.3	2.6	0.7	2.3	0.7	7.6	—

†NG=Non-groupable beta hemolytic streptococci.

*A=Children, age 6-7; B=Children, age 6-8; E=Children, age 6-9; J=Children, age 12-15; R=Adults, Miami residents; NR=Adults, Airline employees, residents and non-residents.

of 32 elementary schools was visited one time only; (2) An additional 100 children (25 in each of four different schools) attending junior high school (grades seven to nine, ages 13-15) were similarly studied each month. In all, 18 junior high schools were visited one time only and seven were surveyed twice during the school year (different children were studied each time). No blood was drawn on members of either of these two age groups; (3) A third section of this year's work was performed on adults residing in the Miami area. During each month, 100 different people had throat cultures and blood samples taken once only. These individuals reported as potential blood donors at the Blood Bank of Mt. Sinai Hospital of Greater Miami, or at the John Elliott Blood Bank, or were visitors at the National Children's Cardiac Hospital; (4) a fourth group of 1015 adults from all areas of the country, in Miami for medical examination for employment, or, for annual physical examination by Eastern Air Lines,* had throat swabbing and venipuncture, one time only.

Results

The non-group A beta hemolytic streptococci recovered in the first three study periods (February-May, 1953; October, 1953-May, 1954; October, 1954-May, 1955) from the three baseline study schools demonstrated that there were 190 instances in which a Group B, C, F, G or a non-groupable organism was recovered at least once. An added 190 cultures contained additional strains of these groups from children whose throats were already positive once for these organisms. Thus, 17.4 per cent of the total number of children (1093) had beta hemolytic streptococci other than group A isolated from their throats at least once during the period of the study. If the number of children swabbed per month is considered, rather than the absolute number of children in the study, it is seen that an average of 944 children were studied; the number of positive cultures on this average figure of 944 is 20.1 per cent.

The county-wide school studies (1954-1955, and 1955-1956) when children of different age groups were cultured once only, yielded 105

*Through the kind assistance of Dr. Howard K. Edwards (deceased), Medical Director of Eastern Airlines.

TABLE 2—BETA HEMOLYTIC STREPTOCOCCI, EXCLUSIVE OF GROUP A, ISOLATED FROM 6535 CULTURES FROM WHITE CHILDREN AND 2664 CULTURES FROM NEGRO CHILDREN, FEB. 1953-MAY, 1956, MIAMI, FLORIDA
(Baseline and County-Wide Studies)

Color		White	Negro	Total
No. Cultures Taken		6535	2664	9199
Group B	Number	78	17	95
	Per cent	1.19	0.64	1.03
Group C	Number	95	163	258
	Per cent	1.45	6.12	2.80
Group F	Number	44	19	63
	Per cent	0.67	0.71	0.68
Group G	Number	147	83	230
	Per cent	0.41	0.38	0.48
Totals	Number	391	292	683
	Per cent	5.98	10.96	7.4

strains of beta hemolytic streptococci other than group A organisms from the throats of 1200 children, six to nine years of age, from October, 1954-June, 1955; 104 strains from 798 children, in the same group, were isolated from October, 1955-May, 1956, and, during this same period, 94 strains were cultured from the throats of 801 children, aged 12 to 15. In both baseline and county-wide child studies, groups C and G were the predominent non-group A beta hemolytic streptococci isolated, while group B, non-groupable, and group F organisms were isolated relatively less frequently.

In the study of 800 adults residing in the Miami area, 59 beta hemolytic streptococcal strains other than group A were recovered, during the October, 1955-May, 1956 period; 100 strains were isolated from the throats of 1015 adults, examined in Miami, but residing in all parts of the United States. Resident and non-resident Miami adult studies indicated that group B and non-groupable organisms were recovered more commonly in this age group than in children.

Results of our studies in both children and adults are summarized in Table 1, which indicates that 842 strains of non-group A streptococci were isolated from 11,014 throat cultures. The recovery rate is 7.6 per cent for the four years of study.

In the baseline study, groups B, F, and non-groupable organisms were isolated in approximately the same percentage from the throats of white children as from negroes, while in the county-wide study, group F and non-groupable organisms were found more often among cultures from negro children. However, greatest differences between the percentages of streptococcal isolates from the two races were recorded for groups C and G organisms. In the baseline studies, group C percentage of isolates were 1.18 for whites, and 5.24 for negroes; percentages in the county-wide studies were 1.93 for whites and 10.82 for negroes. Group G percentages of isolates in the baseline studies were 1.35 for whites and 2.22 for negroes; county-wide studies percentages for whites of 3.82 and 7.93 for negroes. Results of both baseline and county-wide studies of children are summarized in Table 2, which again indicates the marked differences between percentages of groups C and G organisms recovered from white as compared with negro children. In all, non-group A beta hemolytic streptococci were isolated approximately twice as often from the throats of negro as from white children.

Discussion

Eight hundred forty-two strains of beta hemolytic streptococci, other than group A organisms, were isolated from 11,014 throat cultures (7.6 per cent), between February, 1953 and May, 1956. The frequency of recovery of group B, C, F, G and non-groupable streptococcal strains in our studies, when correlated with the elevated average antistreptolysin O titers and indices observed in sera of subjects harboring the streptolysin O producing organisms (groups C and G, possibly certain group F and non-groupable organisms[6]) suggested that these bacteria might be of some pathogenic importance. We have observed that streptococci of groups B, C, F and G were isolated sometimes from the throat cultures taken from patients having symptoms of sore throat, temperature, and other clinical evidence of illness.[7] None of the children in our baseline investigations developed overt symptoms of rheumatic fever or glomerulonephritis.[1-3,8]

No marked differences were observed in frequency of the different groups of non-group A beta hemolytic streptococci at different population age levels. Within the six to nine year age category, however, group C organisms were recovered four to five times as commonly from negroes as from whites. The isolation of non-group A strep-

tococci approximately twice as frequently from the throats of negro as of white children is due almost entirely to the difference in group C isolation rates from the two races. White children's throats yielded beta hemolytic streptococci belonging to groups B, F, G or non-groupable, in 4.5 per cent of the cultures taken; negro children's in 4.8 per cent.

The predominance of group C streptococci in negroes' throats was the only marked racial differential observed in our investigations. Group G organisms were isolated somewhat more commonly from cultures taken from the throats of negro children, but not to the same extent as group C streptococci, while group B streptococci were recovered slightly more frequently from the white children. Group F and non-groupable strains were obtained with equal frequency from white and negro children. Group A organisms have shown no consistent difference in isolation rates in cultures taken from white and negro children.[1-5]

The high rate of recovery of beta hemolytic streptococci other than group A, leads us to call attention to the advisability of the physician obtaining grouping data whenever beta hemolytic streptococci are isolated from the throat of any patient. Information on grouping may be important because of the accepted role of group A organisms as a minor criterion (Jones criteria, modified[9]) in the diagnosis of acute rheumatic fever.

SUMMARY

The recovery of 842 strains of non-group A beta hemolytic streptococci, from 11,014 throat cultures taken from children and adults participating in studies in Dade County, Florida, between February 1953 and May 1956, indicated that these organisms were common in South Florida.

Group A, B, F, and non-groupable organisms were isolated from the throats of white and negro subjects with approximately equal frequency, while group G organisms were recovered somewhat more frequently from throat cultures from negro than from white children. Throat cultures from negro children yielded group C beta hemolytic streptococci four to five times as freqeuntly as did cultures from white children.

The necessity for grouping beta hemolytic streptococcal isolates is emphasized and discussed in order to differentiate non-group A from group A organisms. Non-group A strains are common, they may be related to respiratory illness, and they may confuse the physician in his evaluation of a streptococcal isolate as one of the minor diagnostic criteria of rheumatic fever.

RESUMEN

El haber encontrado 842 cepas de estreptococo no perteneciente al beta hemolítico en las faringes de 11.014 niños, y adultos del Condado Dade de Florida entre Febrero de 1953 y Mayo de 1956, indica que estos gérmenes son comunes en el Sur de Florida.

Se encontraron esos organismos de los grupos A, B, y F, así como otros fuera de grupo identificable en las gargantes de individuos de raza blanca y negra con igual frecuencia, en tanto que gérmenes del grupo G se encontraron con alguna mayor frecuencia en los niños negros que en los blancos. Los cultivos de gargantes de los niños negros van presentados estreptococos beta hemoliticos, grupo C, con una frecuencia de cuatro a cinco veces mejor que la de los niños blancos.

La necesidad de estudiar los grupos de estreptococo hemolitico aislado se destaca y se discute a fin de diferenciar los del grupo A de los que no son de ese grupo. Las cepas no agrupables son comunes y pueden estar relacionadas con enfermedades respiratorias y pueden conducir a confusión al estimar el estreptococo aislado como uno de los criterios de menor cuantía para el diagnóstico de le fiebre reumática.

RESUMÉ

La constatation de 842 souches de streptocoques hémolytiques bêta n'appartenant pas au groupe A sur 11.014 cultures obtenues à partir de prélèvements pharyngés chez des enfants et des adultes faisant partie des cas étudiés dans le Comté Dade, en Floride entre février 1953 et mai 1956, prouva que de tels germes étaient communs en Florida du Sud.

Des microbes du groupe A, B, F et ne pouvant être rattachés à un groupe furent isolés dans la gorge de sujets blancs et noirs, avec une fréquence approximativement égale, tandis que les microbes du groupe G furent constatés un peu plus fréquemment dans les cultures des sujets noirs que chez les enfants blancs. Les cultures des prélèvements laryngés pour les enfants noirs fournirent des streptocoques hémolytiques beta du groupe C quatra à cinq fois plus fréquemment que les cultures des enfants blancs.

La nécessité de grouper les prélèvements de streptocoques hémolytiques beta est mise en évidence et les auteurs discutent les moyens de différencier les germes n'appartenant pas au groupe A de ceux lui appartenant. Les souches n'appartenant pas au groupe A sont fréquentes, elles peuvent être liées à une affection respiratoire, et elles peuvent troubler le médecin dans son estimation du prélèvement streptococcique, celui-ci étant un des critères mineurs de diagnostic pour le rhumatisme articulaire.

ZUSAMMENFASSUNG

Der Fund von 842 Stämmen mit beta-hämolytischen Streptokokken die nicht der Gruppe A angehörten, unter 11014 Halsabstrichen und Kulturen von Kindern und Erwachsen, Teilnehmern an Untersuchungen im Kreis Dade in Florida zwischen Februar 1953 und Mai 1956 bewiesen, daß diese Erreger in Südflorida häufig vorkommen.

Keime der Gruppen A, B, F und nicht bestimmbare Keime liessen sich aus Halsabstrichen gewinnen von Weißen und Farbigen in ungefähr gleicher Häufigkeit, während Keime der Gruppe G mit etwas grösserer Häufigkeit festgestellt wurden in Kulturen von Halsabstrichen von schwarzen als von weißen Kindern. Halsabstriche von schwarzen Kindern ergaben beta-hämolytische Streptokokken der Gruppe C 4-5 mal häufiger als dies bei Kulturen von weißen Kindern der Fall war.

Es wird die Notwendigkeit der Eingruppierung der gezüchteten beta-hämolytischen Streptokokken hervorgehoben und diskutiert zwecks Differenzierung zwischen Keimen der Gruppe A und nicht A. Stämme der Gruppe nicht A sind häufig, sie können in Beziehung gesetzt werden zu Erkrankungen der Atmungsorganen und sind geeignet, bei dem Arzt Verwirrung zu stiften hinsichtlich der Bewertung von Befunden von Streptokokken als von geringerem diagnostischen Wert bei rheumatischem Fieber.

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Congenital Aneurysms of the Aortic Sinuses with Cardioaortic Fistula*

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In 1839, James Hope in "A Treatise on Diseases of the Heart and Great Vessels" described the first recorded case of a congenital aneurysm of the aortic sinuses (sinuses of Valsalva) with rupture into the right side of the heart.[1] The patient, "on lifting a sack of flour, felt a creak in the heart" and died shortly thereafter.

In 1840, Thurnam[2] reported Hope's case in more detail and added five more cases of aortic sinus aneurysms, none of which had ruptured at time of autopsy. The number of congenital aortic sinus aneurysms described in the literature mounted slowly. Maude Abbott was able to accumulate nine cases in 1919,[3] only 12 by 1936.[4] With the advent of the last decade, however, cases began to be reported with an ever increasing frequency. In 1949, Morgan Jones and Langley[5] collected 25 cases from the literature. By 1957, Sawyers, Adams, and Scott[6] had accumulated 45 autopsied cases and two living patients whose lesions had been verified by clinical and roentgenologic methods.

Late in 1957, Lillehei, Stanley, and Varco[7] reported successful surgical closure of ruptured congenital aortic sinus aneurysms in three patients, all of whom demonstrated complete clinical recovery with disappearance of symptoms. The fact that this lesion is now susceptible to curative surgical correction argues for an analysis of the pathogenesis of the lesion and the clinical findings which may aid in its detection.

Since Sawyer's recent summary, 24 more cases have appeared in the literature.[7-29] To his 47 and these 24 are added seven cases culled from the records of the University of Minnesota Hospitals. These 78 patients form the basis of this communication.

Anatomy of the Aortic Sinuses

The three slight dilatations of the aorta situated immediately above corresponding valve cusps are known as the aortic sinuses or sinuses of Valsalva. The nomenclature of these sinuses is somewhat confused in the older literature, but Walmsley's[21] terminology has become widely accepted in recent years and will be employed here; he suggested that sinuses related to the coronary arteries should be named right and left coronary sinuses, the third sinus being called the non-coronary sinus.

The aortic sinuses are almost entirely intracardiac and lie near important parts of the heart[22,23] (Figure 1). The right coronary sinus lies in juxtaposition to the right atrium and right ventricle and actually projects into the conus (outflow tract) of the right ventricle. The left sinus is external to the right ventricle and internal to the pericardial

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sac, being bounded by pericardium only in its posterior half. The non-coronary sinus lies anterior to the left and right atrium, projecting into the latter.

Between the aorta and the main body of the left ventricle there is a tubular zone of fibrous tissue, the annulus fibrosus, which forms an important part of the wall of the aortic sinuses. It extends downward to become incorporated in the wall of the left ventricle and is continuous

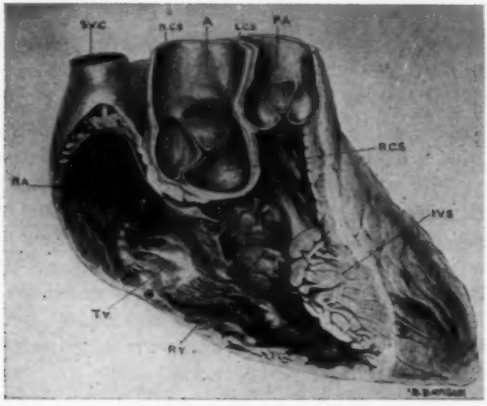

FIGURE 1: Anatomy of the aortic sinuses. The anterior part of the interventricular septum (I.V.S.) has been sectioned. The right coronary sinus (R.C.S.) projects into the outflow tract of the right ventricle (R.V.). The non-coronary sinus (N.C.S.) projects into the right auricle (R.A.), and the left coronary sinus (L.C.S.) with its coronary artery can be seen postero-laterally. (From Morgan Jones, A., and Langley, F.A.: "Aortic Sinus Aneurysms," *Brit. Heart J.* 11:325, 1949).

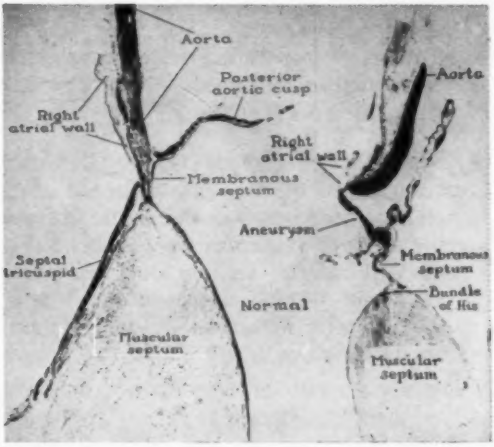

FIGURE 2: Longitudinal sections through the non-coronary aortic sinus and adjacent structures. (A) Normal heart. The posterior sinus is in close proximity with the right atrial wall. The media of the aorta is continuous with the annulus fibrosus. (B) Non-coronary sinus congenital aneurysm which perforated into the right atrium. The mouth of the aneurysm represents a lack of continuity between the aortic media and the annulus fibrosus at this site. The main wall of the aneurysm is formed by atrophic right atrial wall. (From Edwards, J. E., and Burchell, H. B.: "Specimen Exhibiting the Essential Lesion in Aneurysm of the Aortic Sinus," *Proc. Staff Meet., Mayo Clin.* 31:407, 1956.)

superiorly with the elastic tissue of the aortic media. Edwards and Burchell[24] have shown that the essential lesion in congenital aneurysm of a sinus of Valsalva is a lack of continuity between the annulus fibrosus and the media of the aorta with its strength giving muscular and elastic tissue (Figure 2). The aneurysm is usually a cone shaped extension of fibrous tissue with a small ostium, often no larger than one centimeter in its widest diameter, and an even smaller perforation at its apex.[8]

The right coronary sinus is by far the most common site of origin for a congenital aneurysm (Tables 1 and 2). Forty-two of the 55 cases with rupture of the aneurysm and eight of the 19 unruptured aneurysms originated in this location. Of the 42 which ruptured, 31 created cardioaortic fistulas into the cavity of the right ventricle and only five communicated with the right atrium. This is not an unlikely circumstance when one considers that the normal undilated right coronary sinus actually projects into the outflow tract of the right ventricle. In one case there was perforation into the pulmonary artery and there are two recorded instances of communication with the pericardial sac. Only two of the 41 fistulae emptied into the left ventricle, a reflection of the much narrower pressure gradient between the aorta and the left ventricle as compared with the right side of the heart.

Sixteen ruptured congenital aneurysms of the non-coronary sinus have been reported; all have perforated into the right heart, 13 into the right atrium (the normal non-coronary sinus projects into this chamber) and three into the right ventricle.

One of our patients (L.G., case 8) at autopsy was found to have a fistulous aneurysmal tract from the left coronary sinus leading into the right atrium. Although the literature records two instances of unruptured aneurysms of the left sinus, this case is, to our knowledge, the first recorded ruptured left sinus congenital aneurysm.

Among the unruptured aneurysms, the most common finding is a generalized dilatation of all three sinuses.[17,19,25,26] Numerous autopsy reports in patients with ruptured congenital aortic sinus aneurysms make mention of dilatation and even aneurysm formation in the other sinuses uninvolved by rupture, and it appears quite likely that the congenital weakness involves all three sinuses in many if not most cases. In two recorded cases, there was aneurysmal dilatation of the right and noncoronary sinuses, the left sinus was normal, and only the right had

TABLE 1—RUPTURE OF CONGENITAL ANEURYSMS OF THE SINUSES OF VALSALVA: SITES OF ORIGIN AND TERMINATION OF CARDIOAORTIC FISTULA IN 59 CASES

Site of Origin:		Site of Termination:	
Right Coronary (Aortic) Sinus	(42)	Right Ventricle	31
		Right Atrium	5
		Right Atrium and Right Ventricle	1
		Left Ventricle	2
		Pulmonary Artery	1
		Pericardial Sac	2
Non-Coronary Sinus	(16)	Right Atrium	13
		Right Ventricle	3
Left Coronary (Aortic) Sinus	(1)	Right Atrium	1

perforated.[27,33] In another instance, both the right and non-coronary sinuses had perforated, the left remaining intact.[29]

While congenital aneurysm of the aortic sinuses is often an isolated lesion, this is by no means always the case. Basabe, Hojman, and Rosenblit[30] found that the lesion coexisted with a bicuspid aortic valve in six of 26 cases reported in the literature to that time. Morgan-Jones and Langley[5] discovered 10 concomitant interventricular septal defects in 25 cases. Coarctation of the aorta coexisted in two of this group. More recently, Dubilier, Taylor, and Steinberg[25] have reported three cases of coarctation associated with generalized dilatation of all three sinuses; they state that the increased pressure in the aorta proximal to the coarctation magnifies the congenital weakness of the elastic tissue at the base of the aorta and makes early aneurysm formation and rupture more likely.

In 1955, Steinberg and Geller[19] reported three cases of generalized aneurysmal dilatation in patients with Marfan's syndrome, an unusual symptom complex in which the most striking abnormality is arachnodactyly, long thin bones with tapering fingers. The palate is high and arched, the skull is dolichocephalic and dislocation of the lens is a common finding. This is a dominant hereditary disorder which is believed to involve a disturbance in the metabolism of chondroitin sulfate, the ground substance of connective tissue. These patients often exhibit medial degeneration of the aorta with early aneurysmal dilatation of the ascending aorta. In 1956, Steinberg and Finby[17] recorded four more patients with Marfan's syndrome and generalized aneurysmal dilatation of the aortic sinuses.

TABLE 2—UNRUPTURED CONGENITAL ANEURYSMS OF THE SINUSES OF VALSALVA: SITE OF ORIGIN IN 19 CASES

Generalized aneurysmal dilatation of all three aortic sinuses	9
Right Coronary Sinus	8
Left Coronary Sinus	2
Non-Coronary Sinus	0

Pathogenesis

In 1912, Mall[21] first proposed a causative mechanism for this anomaly. He theorized that congenital aneurysms resulted from incomplete fusion of the proximal and distal swellings of the bulbus cordis. Complete failure of fusion would lead to a high interventricular septal defect (membranous portion), while incomplete fusion would lead to an attenuation of the tissues at the base of the aorta. These, Mall states, are liable to early dilatation and aneurysm formation due to the constant stress of the aortic pulse.

Venning[32] takes issue with this theory. He points out that fusion between the proximal and distal bulbar swellings occurs about the seventh week of fetal development, long before the tissues of the fetal heart have undergone differentiation. Since Edwards and Burchell[34] have shown that the histopathology of the lesion is a defect in the elastic tissue in the base of the aorta, the etiologic process could not have occurred before the time of differentiation of the elastic tissue.

Our present day concept of the pathogenesis of congenital aneurysms of the aortic sinuses must be twofold: 1) defective development of the elastic tissue at the base of the aorta, and 2) the constant stress of aortic pulsation on this weakened area.

Abbott[3] and Brown and Burnett[32] have reported cases in which autopsy has disclosed little or no aneurysmal tissue, only an endothelialized tract leading from an aortic sinus to the outflow tract of the right ventricle. In each case, the clinical history was compatible with an intracardiac shunt present at the time of birth. Four of our cases (Nos. 1, 2, 3 and 6) were found at operation to have no aneurysmal tissue, only the defect in the aortic sinus. All of these had continuous murmurs discovered shortly after birth and became symptomatic early in life.

Certain aneurysms of the aortic sinuses are clearly acquired in origin. These mycotic lesions are secondary to either a bacterial endocarditis or a chronic syphilitic process. In this series of patients we are not concerned with acquired aneurysms. In these patients, there has been no evidence of congenital or acquired lues, the syphilitic serologies were routinely negative, and there has been no calcification in the aorta or the aortic sinuses, with the exception of those cases where subacute bacterial endocarditis or atherosclerotic changes were superimposed on a congenital aneurysm.

Case Reports

Three of our cases [No. 1 (D.D.), No. 5 (S.W.), and No. 10 (B.M.)] have been reported previously by Lillehei, Stanley, and Varco.[7] Table 3 is intended to accompany these case reports and provide the reader with a concise comparison of findings.

Case 1: This is a ten year-old girl, a product of a normal pregnancy and delivery. After birth, however, she failed to gain weight and suffered a persistent upper respiratory infection. On examination at six months of age, a heart murmur was heard, but no cyanosis or dyspnea was noted. The child continued to show slow development with easy fatigability and failure to gain weight. In 1953, at age seven, grade IV rough systolic and grade II diastolic murmurs of a machinery quality were heard. The blood pressure was 130/50. It was felt that she had a patent ductus arteriosus and such a structure was divided; however, the murmurs and symptoms persisted. In 1956, she was admitted to the University of Minnesota Hospitals. At age 10, she weighed only 32 pounds. She was not cyanotic. The clinical data at this time are shown in Table 3. The diagnosis was made preoperatively from the typical clinical and catheterization findings. At operation, no aneurysm was seen but a fistulous communication with "excess fibrotic tissue" was found between the right aortic sinus and the right ventricle. This was closed with sutures, and the patient made excellent progress and is now asymptomatic.

Case 2: This eight year-old boy was the product of a normal pregnancy, but a prolonged (38 hours) delivery. From birth on, he manifested signs of respiratory infection and a murmur was heard at five weeks of age. However, the respiratory infection did not persist and the boy showed good growth and was never dyspneic or cyanotic. On his second hospital admission at age seven, it was stated that he was bothered by more upper respiratory infections than his peers or siblings. He showed a slight precordial bulge with a systolic thrill at the left sternal border and at the suprasternal notch. Grade IV systolic and grade III diastolic murmurs were maximal in the third left intercostal space. Catheterization (Table 3) showed a jump in the oxygen saturation at the ventricular level. The pressure in the right ventricle was 105/0, an infundibular pressure curve was obtained, and pulmonary artery pressure was 25/15. At operation one year later, no aneurysm was found but a defect about 5 millimeters in diameter was seen in the non-coronary sinus, communicating with the right ventricle. This was closed and the pulmonary infundibular stenosis was resected. The boy made an uneventful recovery from surgery.

Case 3: This nine year-old boy was noted to have a heart murmur at birth, but his parents were told he would "outgrow" it. He was asymptomatic until age one when he began to manifest signs of desaturation — episodes of cyanosis, squatting, and dizziness. These symptoms continued along with progressive dyspnea on exertion and mild growth retardation. He never was heard to have a continuous murmur, only a grade III systolic murmur maximal in the third left intercostal space. The findings (Table 3) were felt to be consistent with tetralogy of Fallot and he was sent to surgery.

TABLE 3—RUPTURED CONGENITAL ANEURYSMS OF THE S

	1. D.D., *f*	2. B.I., *m*	3. C.L., *m*
Age at last admission	10	8	9
Murmur first heard	6 mo.	5 wk.	birth
Dyspnea and/or pain			
—age of onset	6 mo.	none	1
—was onset sudden?	no		no
Admission blood pressure	100/0	120/60	100/60
Continuous murmur maximal	3 RICS	3 LICS	none
Electrocardiogram	LVH, LVS	LVH, LVS	RVS
Roentgen findings			
—prominent pulmonary artery segment	yes	yes	no
—active aortic pulsation	yes	yes	yes
—pulmonary vascular markings	increased	increased	normal
—chamber enlargement	RV, LA, LV	RV, LA, LV	none
Catheterization data (% saturation)			
—superior vena cava	69	69	—
—right atrium	67	68	—
—right ventricle inflow	—	76	—
—right ventricle outflow	87	79	—
—pulmonary artery	87	83	—
Thoracotomy for patent ductus	yes	no	no
Communication	R into RV	N into RV	R into RV
Comment	Fistula closed at surgery	Fistula closed at surgery; co-existing infundibular pulmonary stenosis resected, too	Incidental finding with tetralogy of Fallot; closed at surgery but expired postoperatively

L=Left Coronary Sinus RV=Right Ventricle LA =Left Atrium
R=Right Coronary Sinus RA=Right Atrium LVS=Left Ventricular S
N=Non-Coronary Sinus LV=Left Ventricle LVH=Left Ventricular H

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VA: UNIVERSITY OF MINNESOTA HOSPITALS, 1949-58

	6. A.N., *f*	7. M.L., *m*	8. L.G., *f*	9. O.N., *f*	10. B.M., *m*
	17	51	54	44	36
	9	24	7	38	26
	16	31	25	38	36
	no	no	no	no	yes
	160/55	160/50	190/5	120/10	160/40
	4 RICS	4 LICS	4 RICS	4 LICS	5 RICS
	LVS	RBBB	LVH, LVS, RBBB	LVS	LVS
	yes	yes	yes	yes	yes
	yes	no	no	yes	yes
	increased	increased	increased	increased	increased
V, A, LV	RV, LA, LV	LA, LV	RV, LV	RV, LA, LV	RV, LV
	—	—	—	72	50
	70	65	—	90	82
	79	—	—	—	—
	91	90	—	81	83
	86	89	—	84	82
	yes	no	no	no	no
	R into RV	R into RV	L into RA	N into RA	N into RA
ed	Fistula and co-existing inter-ventricular septal defect closed at surgery	Expired; fistula and coexisting interventricular septal defect found at autopsy	Expired	Expired; rheumatic valvalitis, tricuspid and mitral, also found	Fistula closed at surgery

RBBB=Right Bundle Branch Block
ICS =Left Intercostal Space
RICS =Right Intercostal Space

f =female
m=male

On cardiotomy, it was seen that he not only had pulmonary stenosis and interventricular septal defect, but there was also a fistula (again, no aneurysm) between the right aortic sinus and the right ventricle. All the defects were repaired, but the child went into complete heartblock as the cardiotomy incision was being closed. He was treated with Isuprel with good results, but experienced a sudden episode of cardiac arrest on his 19th post-operative day and expired. Autopsy revealed complete closure of all defects.

Case 4: This is an 18 year-old male who was first noted to have a heart murmur at six years of age on a routine school examination. Three years later, in 1939, he was seen at University Hospital and a heaving precordium and machinery murmur were noted. He was subjected to thoracotomy and the ductus arteriosus was ligated. The surgeon at that time stated his doubts as to the patency of this structure, and the murmur persisted after operation. He was essentially asymptomatic, however, until age 16 when he experienced an episode of cardiac decompensation after an upper respiratory infection. The failure persisted despite digitalization and administration of diuretics, and he was again subjected to thoracotomy which revealed no evidence of a possibly recanalized ductus arteriosus. He failed to make a good recovery from this second operation and expired 12 days postoperatively in severe decompensation. Autopsy revealed an aneurysm of the right aortic sinus extending into the right ventricle with a one centimeter tear at its apex. Coexistent with this lesion were a defect of the membranous interventricular septum and a slight coarctation of the aorta distal to the origin of the left subclavian artery.

Case 5: This 19 year-old woman was adopted at the age of one year. Physical examination at that time revealed no murmur or sign of cardiac disease. At age five, she was stricken with arthralgia, fever, epistaxis, and a tendency to fall easily. The diagnosis of rheumatic fever was made when a heart murmur was heard, and the child was immobilized for one year. During the remainder of her childhood, she was extremely limited in her activities by dyspnea, easy fatigability, and poor weight gain. At age 18 she experienced her first attack of angina and this recurred many times with relief from nitroglycerin. Examination at this time revealed high pitched grade III-IV systolic and diastolic murmurs over the tricuspid area. Cardiac catheterization revealed a rise in oxygen saturation at the ventricular level. At surgery, she was found to have an aneurysm from the right aortic sinus into the right ventricle which was perforated at its apex. The fistula was closed and the girl has made an excellent recovery and now has no exercise limitations.

Case 6: This is a 17 year-old girl who was noted to have tachycardia with precordial heave and a murmur at age nine. This was diagnosed as rheumatic fever, and she was immobilized for five months. She was asymptomatic thereafter until age 16. At age 13, thoracotomy was performed but the ductus arteriosus was not patent. At 16 she began having exertional dyspnea and orthopnea. On physical examination one year later, she was found to have a heaving precordium with both systolic and diastolic thrills and a grade IV continuous murmur loudest over the fourth and fifth right intercostal spaces at the sternal border. At surgery, an aneurysm of the right sinus of Valsalva was found to communicate with the right ventricle. There was also a high interventricular septal defect and some insufficiency of the aortic valve. The defects were repaired, but she was left with some aortic insufficiency. She has done well postoperatively.

Case 7: This 51 year-old man was first seen at University Hospital in 1934 at age 31. Seven years earlier, he had been told he had a "leaky heart," but he had been asymptomatic until five weeks prior to admission when he noted the insidious onset of symptoms of congestive heart failure. Examination in 1934 revealed loud systolic and diastolic murmurs maximal in the fourth left intercostal space at the sternal border. He was digitalized and seen on several occasions over the next 20 years for episodes of decompensation. It was one of these episodes which brought about his second admission in 1954. Cardiac catheterization revealed a jump in oxygen saturation at the ventricular level. His course was gradually downhill over a two-month hospital stay and he expired. Autopsy showed an aneurysm of the right aortic sinus which extended into the right ventricle and showed three small perforations at its apex. A coexisting interventricular septal defect was also found.

Case 8: This is a 54 year-old woman who was admitted to Minneapolis General Hospital on 18 occasions. She was never known to have been a blue baby. At age nine, she suffered an attack of "typhoid pneumonia" and was kept at bed rest for nine months. Shortly thereafter, a murmur was heard but she was asymptomatic until age 25, when she began to have episodes of palpitation, precordial pain, and dyspnea on exertion. She did well through her first five pregnancies, but was decompensated during the later months of her last two and sought medical attention on these occasions. It was then (1933, 1937) noted that she had systolic and diastolic murmurs loudest in the fourth right intercostal space at the left sternal border. Other than these last two pregnancies, she did well on digitalis maintenance until 1956. In 1951, an attempt at cardiac catheterization was unsuccessful. During the first eight months of 1956, she followed a rapidly progressive downhill course developing chronic cardiac decompensation and a low salt syndrome. Terminally, she developed cyanosis for the

first time. She expired in August, 1956, and autopsy revealed an aneurysm of the left aortic sinus which had herniated into the interatrial septum and formed a large (3.5 x 1.5 inches) pouch in the septum. An eight millimeter perforation was found in the right wall of this pouch, allowing for communication between the left sinus and the right atrium.*

Case 9: This 44 year-old woman was the product of a normal pregnancy and delivery and breathed well at birth. At age 18, she suffered an attack of arthralgia with fever, but without prior sore throat or joint swelling. No heart murmur was heard at this time or at any time until she reached age 38 when she noted the insidious onset of dyspnea on exertion. One year later, she had a sore throat which was followed by fever, chills, an elevated sedimentation rate, dyspnea, and orthopnea. Two years later, when hospitalized for nasal polypectomy, grade IV high pitched systolic and diastolic murmurs were heard all over the precordium, maximal in the fourth left intercostal space at the sternal border. The blood pressure was 106/60. Catheterization at age 42 revealed a rise in the oxygen saturation at the atrial level. Her shortness of breath worsened, and she went into chronic cardiac decompensation. Shortly before death, she suffered an acute subarachnoid hemorrhage. Her blood pressure at that time was 120/10. She progressed into uremia and died with uremic pericarditis. Autopsy revealed rheumatic valvulitis involving both the tricuspid and mitral values. A thin-walled saccular aneurysm arising from the non-coronary sinus protruded into the right atrium, and two small openings at its apex allowed communication between these chambers.

Case 10: This 36 year-old man was asymptomatic and never known to have a cardiac murmur until age 26, when, on his discharge physical from the Royal Canadian Air Force, a grade II systolic murmur was heard in the fifth right intercostal space at the sternal border. He denied any history of rheumatic fever, but voluntarily moderately limited his activities for the next 10 years despite lack of symptoms. Examination at age 30 revealed a normal electrocardiogram and a blood pressure of 150/80. At age 36, in 1956, he was stricken suddenly by severe upper abdominal pain and dyspnea on moderate exertion. Examination revealed a grade IV "to and fro" murmur loudest in the above location. He was found to be in heart failure and was hospitalized. Despite continuous hospitalization for the next six months, he remained in intractable failure. Cardiac catheterization demonstrated a rise in oxygen saturation at the atrial level. He was transferred to University Hospital and operated in December of 1956. Operative findings included fluid in the pericardial and right pleural cavities and an aneurysm of the non-coronary sinus projecting into the right atrium with a two centimeter opening at its apex. The aneurysm was excised, the fistula closed by sutures, and he made an uneventful recovery from surgery. Two years after his surgery, he is doing well and living an active normal life.

Clinical Features

Clinical manifestations of congenital aneurysms of the aortic sinuses are chiefly related to the sequelae of rupture of the aneurysm. These aneurysms occur much more frequently in males than in females; 80 per cent of the reported cases were in men, although the ratio was 5:5 in our group of 10 patients at the University of Minnesota Hospitals (Table 3).

The range of age of onset of symptoms is wide, varying in our patients from six months to 41 years. Often the patient has been told he has a heart murmur, but has remained asymptomatic for many years. Mild dyspnea and palpitations are not unknown in patients with unruptured aneurysms, however. In the literature, sudden onset of dyspnea and chest pain is reported as characteristic of rupture of the aneurysm, this event often being related to severe stress or strain. However, rupture may take place while the person is completely at rest. Breathlessness was common to all cases, but many did not manifest the usual substernal or upper abdominal pain. The pain when it does occur is said to simulate that of myocardial infarction, but does not radiate to the neck, arms, jaw, or back.[4] The dyspnea and pain usually last several hours, relenting gradually and leaving the patient almost asymptomatic again. If rup-

*The authors wish to thank Dr. John Coe and Dr. Aaron Mark of the Department of Pathology of Minneapolis General Hospital for permission to cite the history and autopsy data of this case.

ture has occurred into the pericardial sac, however, death is usually immediate.

Rupture of the aneurysm is often not as sudden and dramatic as described above. In at least 30 per cent of the reported cases and in nine of our 10 patients, the onset of symptoms was insidious. Frequent respiratory infections, gradually increasing ease of fatigability, and progressively worsening dyspnea were the rule in this group. If the patient was a child, his physical growth was often retarded.

After rupture of the aneurysm, the patient may remain asymptomatic for a few months or, more commonly, years. Towards the end of this period, gross manifestations of a combination of aortic and tricuspid insufficiency often become evident. The pulse is collapsing in nature and the pulse pressure is very wide, indicating the rapid aortic runoff. The cervical veins expand with ventricular systole, and a pulsatile liver has been reported in many cases.

Although the patient is dyspneic, he does not manifest cyanosis unless congestive heart failure supervenes. Examination of the heart reveals a prominent systolic thrill localized to the fourth and fifth intercostal spaces at the right or left sternal border, more commonly the right. Auscultation reveals a continuous murmur, which is loud and superficial and often has a machinery-like quality (Figure 3). It is maximal in midsystole, and wanes around the second heart sound only to wax again in mid-diastole. It is heard maximally along the right or left border of the sternum, usually in the third, fourth, or fifth intercostal spaces (four of our six cases), but is transmitted all over the precordium.

This machinery-like murmur is most often confused with that of a patent ductus arteriosus. Three of our cases had undergone thoracotomy for planned ligation and division of a patent ductus. The characteristic ductus murmur, however, is heard maximally in the second left intercostal space beneath the clavicle. It crescendos up to the second sound, then gradually decreases in amplitude throughout diastole, and lacks the superficial quality of a ruptured aortic sinus murmur.

Both Brown[35] and Falholt and Thomsen[34] have reported patients with unruptured congenital aneurysm of an aortic sinus, who manifest a continuous murmur identical in nature to that described above for the

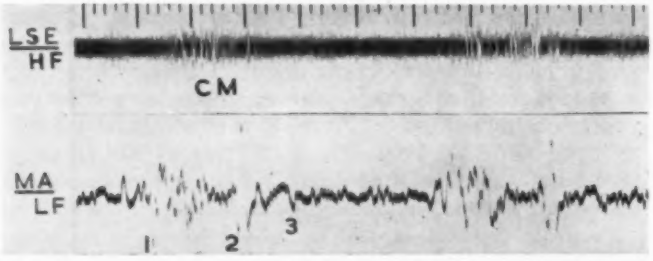

FIGURE 3: Phonocardiogram in a patient with a fistula from the right aortic sinus into the right ventricle. The continuous murmur (CM) is greatest in mid-systole, wanes about the second heart sound (2), only to wax again in mid-diastole. LSE—left sternal edge, MA—mitral area, HF—high frequency, LF—low frequency. (From Neill, C., and Mounsey, P.: "Auscultation in Patent Ductus Arteriosus with a Description of Two Fistulae Simulating Patent Ductus," *Brit. Heart J.* 20:61, 1958.)

rupture lesion. Most other authors cite only a systolic murmur before rupture, however, and this is our clinical impression.

Electrocardiographic Findings

The electrocardiogram is not often of diagnostic aid. Creation of a large left-to-right shunt through the cardioaortic fistula places an increased work load on the left ventricle and results in a left ventricular strain or left ventricular hypertrophy pattern. Eight of our 10 patients manifested one or the other pattern. In at least one case,[35] rupture of the aneurysm produced the electrocardiographic changes characteristic of acute myocardial insufficiency, and autopsy revealed severe ischemia of the heart muscle. Warthen[36] has reported a case of a congenital aneurysm of the right coronary sinus which protruded down into the membranous interventricular septum and produced a right bundle branch block pattern, which he felt was due to encroachment of the aneurysm on the atrioventricular node or bundle. One of our patients (No. 7), who also had an interventricular septal defect, manifested the same pattern. Duros[37] recorded a case of rupture of a non-coronary sinus aneurysm into the right atrium in which the patient was in complete heart block. Both he and Micks,[38] who had a similar case but without rupture of the aneurysm, feel that the heart block was a result of pressure on the atrioventricular node and bundle of His. The electrocardiogram may occasionally be normal.

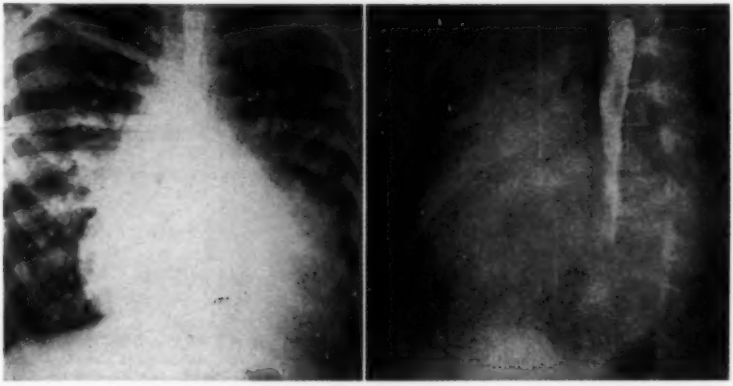

FIGURE 4: Preoperative roentgenograms of ten year old girl (No. 4 on Table 3) with rupture of right aortic sinus aneurysm into the right ventricle. There is marked cardiomegaly. Advanced left ventricular enlargement is demonstrated in the oblique view.

Roentgenographic Findings

Chest roentgenograms of the patient with an isolated unruptured congenital aortic sinus aneurysm are usually normal. With rupture and creation of cardioaortic fistula, the left ventricle begins to enlarge, then the left atrium, then the right side of the heart. The initial chest film usually shows generalized cardiomegaly (Figure 4), but reveals no finding which is pathognomonic of this lesion. The pulmonary vascular markings are often increased far above the limits of normal (nine of our 10 cases). Kjellberg,[10] in his report of two cases, noted that while the

ascending aorta appeared dilated on the roentgenogram, the aortic arch was narrow in both instances, in marked contrast to its appearance in patent ductus arteriosus. No other author has made mention of this sign, but it was noted in three of our 10 cases (Nos. 4, 5, and 6).

Cardiac fluoroscopy usually reveals active pulmonary artery pulsation, and occasionally hilar dance is noted. In most cases, the aorta too exhibits very active pulsations. In Case 3, where nearly all the clinical information pointed to uncomplicated tetralogy of Fallot, active aortic pulsations were remarkable.

The definitive diagnosis of congenital aneurysm of an aortic sinus requires special roentgenographic procedures. Steinberg[17] has employed angiocardiography in the diagnosis of some 14 cases. With the use of contrast medium injected into a peripheral vein under pressure, he has demonstrated filling of aneurysmal dilatations at the root of the aorta just above the aortic valve after the dye has been circulated through the lungs, returned to the left heart, and expelled by the left ventricle. He points out that the left anterior oblique projection is the most useful for diagnosis; in this view the right coronary sinus, most commonly involved with aneurysm and fistula formation, is anterior to the heart and just behind the sternum. Brofman and Elder[5] demonstrated a cardioaortic fistula with angiocardiography aided by temporary circulatory occlusion; for 15 seconds, the neck veins were occluded by compression and the inferior vena cava by a balloon tipped catheter, thus enabling visualization of the contrast medium as it passed through the fistula.

Falholt and Thomsen[24] were the first to employ retrograde aortography in the demonstration of aortic sinus aneurysms. Their patient had an unruptured right aortic sinus aneurysm which appeared as a chamber below and in front of the aorta but deeply situated in the heart shadow, thus ruling out a coronary artery aneurysm. Lin, Crockett, and Dimond[11]

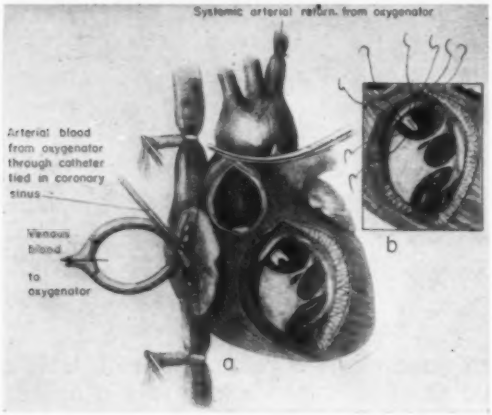

FIGURE 5: Operative approach for direct vision repair of rupture of right aortic sinus aneurysm into the right ventricle (case 4, in Table 3). *a*. The heart and lungs have been totally bypassed utilizing the pump-oxygenator. Aortotomy and ventriculotomy permit complete exposure of aneurysmal sac and perforation. The myocardium is oxygenated and coronary air embolism is avoided by retrograde perfusion of the coronary veins. *b*. Surgical repair. (From Lillehei, C. W.; Stanley, P., and Varco, R. L.: "Surgical Treatment of Ruptured Aneurysms of the Sinus of Valsalva," *Ann. Surg.* 146:459, 1957.)

performed retrograde aortography on a patient with cardioaortic fistula, but the patient experienced an untoward reaction to the contrast agent and died in circulatory collapse. Murrow[16] has used this procedure to diagnose two ruptured congenital aneurysms, and neither he nor Falholt and Thomsen have experienced untoward reactions on their patients.

Cardiac Catheterization

After rupture of an aortic sinus aneurysm with creation of a cardioaortic fistula into the right heart, a left-to-right shunt of considerable magnitude is created. Taussig[28] states that the main flow of the aorta into the right side of the heart occurs in diastole when the myocardium is relaxed and the fistulous ostium is thus widely patent. The result is a marked increase in pulmonary flow and a rise in pressure in the chamber into which the aneurysm perforates and in all chambers distal to the perforation.

Cardiac catheterization reflects these changes (Table 3). There is a marked rise in both oxygen saturation and pressure of the blood in the right atrium or the right ventricle, depending on which chamber has been perforated. Most commonly the fistula is into the outflow tract of the right ventricle and this is reflected in marked elevation of oxygen saturation and pressure at this point and in the pulmonary artery. If the rise has occurred in the right atrium and the patient has a continuous murmur low along either sternal border, the diagnosis can be made with impunity.

If the patient survives for a sufficiently long period of time after rupture of the aneurysm, the pulmonary vascular bed responds in a typical manner to the stress of the altered hemodynamics. Brown[29] noted marked medial hypertrophy and fibrous and elastic intimal proliferation in a patient who died nine years after a typical episode of dyspnea and chest pain. Clinically, these changes in the pulmonary vascular bed are reflected in the development of pulmonary hypertension and right ventricular hypertrophy.

Prognosis

The prognosis in the patient with unruptured congenital aneurysm of a sinus of Valsalva is uncertain. It is apparent that the lesion is compatible with survival into the adult age group. In Sawyer's review,[6] the average age of rupture of the aneurysm was 31 years. In the eight cases who died with the aneurysm intact, the mean age of death was 33 years.

After rupture of the aneurysm, the patient often enters an asymptomatic phase, as described above. The length of this phase is variable, ranging in the cases reported in the literature from immediate death (rupture into pericardial sac) to 15 years. In the end, the patient succumbs to congestive heart failure or subacute bacterial endocarditis. The former is the more common cause, but modern medical therapy has kept many patients alive for years after the rupture.

Differential Diagnosis

The differential diagnosis of congenital aortic sinus aneurysm with rupture creating a cardioaortic fistula is that of a patient with dyspnea

and/or chest or upper abdominal pain who reveals a continuous murmur on auscultation of the heart. It includes:

1. Patent ductus arteriosus.
2. Aortic pulmonic window.
   In these two lesions, as described above, the nature and location of the murmur differs from that of a ruptured aortic sinus aneurysm. Cardiac catheterization reveals significant elevation in oxygen saturation in the pulmonary artery, but not in the right ventricle or the right atrium.
3. Interventricular septal defect with aortic insufficiency.
   Clinical differentiation may prove exceedingly difficult and angiocardiography or retrograde aortography must be employed for definitive diagnosis. Burchell and Edwards[39] have reported autopsy findings of rupture of a right aortic sinus aneurysm into the right ventricle on a patient diagnosed and even reported in the literature as interventricular septal defect with aortic insufficiency.
4. Pulmonary arteriovenous fistula.
   The murmur here is seldom as harsh and may disappear on performance of the Valsalva maneuver. Definitive differentiation requires angiocardiography.
5. Coronary arteriovenous fistula.[40]
   Findings on clinical examination and cardiac catheterization may be idential with those of a ruptured congenital aortic sinus aneurysm. Again, definitive diagnosis requires angiocardiography or retrograde aortography.
6. Venous hum.
   Occasionally, this may be loud enough to simulate a continuous murmur. Compression of the neck veins will lessen the hum.

Surgical Correction

Successful surgical correction of a ruptured aortic sinus aneurysm awaited the advent of extracorporeal circulation with a pump-oxygenator. Lillehei, Stanley, and Varco[8] in 1957 reported closure of three cardioaortic fistulae (Cases 1, 5, and 10), and since that time have successfully closed two more under direct vision; all five have shown marked clinical improvement post-operatively with disappearance of their murmurs and restoration of unlimited physical activity. None of the three has demonstrated residual symptomatology or recurrence of symptoms in the 12 to 36 months since their surgery.

Murrow[41] has also performed successful surgical closure of ruptured congenital aortic sinus aneurysms in two cases utilizing the pump-oxygenator. Both fistulae originated in the right aortic sinus, one communicating with the right ventricle and one with the right atrium. Cooley[14] too has corrected this otherwise inevitably fatal condition under direct vision with the pump-oxygenator. In his case, the communication was from the right sinus into the right ventricle.

Utilizing total cardiopulmonary bypass, the surgeon is able to attack the fistula under direct vision, to resect the redundant aneurysmal tissue, and to place his sutures closing the communication in such a manner as to approximate the annulus fibrosus of the aortic valve to the aorta. Retrograde coronary sinus perfusion and potassium citrate asystole are

employed in conjunction with the pump-oxygenator to prevent myocardial anoxia and coronary air embolism[42] (Figure 5).

In the three years prior to these reports of successful surgical correction, seven cases of unsuccessful surgical treatment had been recorded in the literature, with six deaths[1,8,13,15,38,42] and one instance of incomplete closure of the fistula in which the patient survives with residual symptomatology.[12]

Repair of an unruptured congenital aneurysm of a sinus of Valsalva has yet to be reported in the literature. With the gradually increasing acceptance of "open heart" surgery and the progressively declining mortality of these procedures, clinical and angiocardiographic or aortographic identification of an unruptured aneurysm may soon be an absolute indication for its correction. At present, rupture of such an aneurysm constitutes an indication for closure; in all but the rare instances of perforation into the pericardial sac, there is adequate time to prepare the patient for surgery after the episode of rupture.

SUMMARY

1. Although congenital aneurysms of the aortic sinuses (of Valsalva) are of rare occurrence, 71 cases of this defect have been reported in the literature. Ten patients from the University of Minnesota Hospitals with clinical or autopsy evidence of this malformation are also included in this report.

2. Of the total of 78 cases, 59 had undergone rupture of the aneurysm with creation of a cardioaortic fistula. The most common site of termination was the right ventricle (34 cases).

3. Symptomatology of this lesion is described. The essential lesion is a lack of continuity between the annulus fibrosus of the aortic valve and the elastic aortic media. In at least six cases, clinical history and autopsy findings are compatible with a cardioaortic fistula present at birth. Most commonly the unruptured aneurysm is relatively asymptomatic, the patient being aware only of a heart murmur or mild dyspnea. In contradiction to repeated impressions in the literature, rupture of the aneurysm was not a sudden dramatic event in nine of our ten cases. The typical continuous murmur heard after rupture is differentiated from that of patent ductus arteriosus by location and quality. Findings on the electrocardiogram and roentgenogram and at cardiac catheterization are reviewed. The definitive diagnosis can be made by angiocardiography or retrograde aortography.

4. Successful surgical closure of a ruptured congenital aortic sinus aneurysm has been reported in eight cases within the past two years utilizing cardiopulmonary bypass with a pump-oxygenator and retrograde coronary perfusion. Rupture of the aneurysm does not result in immediate death (except in the extremely rare instances of rupture into the pericardial sac). The usual patient can be carried on medical therapy for several years, if need be. However, with the availability of the pump-oxygenator, definitive demonstration of a cardioaortic fistula must be considered a strong indication for its closure under "open heart" techniques.

RESUMEN

1. Aunque los aneurismas congenitos de los senos aórticos (de Valsalva) son raros, se han relatado en la literatura 71 casos. Se incluyen en este trabajo diez enfermos de los hospitales de la universidad de Minnesota con evidencia clínica o de autopsia.

2. Del total de 78, 59 casos sufrieron ruptura del aneurisma con la creación de una fístula cardioaórtica. El lugar más común de desembocadura fué el ventrículo derecho (34 casos).

3. Se describe la sintomatología de esta lesión. La lesión en esencia consiste en una falta de continuidad entre el anillo fibroso de la válvula aórtica y la cama elástica media aórtica. Por lo menos en seis casos la historia clínica y los hallazgos de autopsia fueron compatibles con una fístula cardioaórtica existente al nacer. Más conmunmente el aneurisma sin ruptura es relativamente asintomático, notando sólo el enfermo, un murmullo cardiaco o moderada disnea.

Contrariamente a los asentado en la literatura repitidamente, la ruptura del eneurisma no fué un acontecimiento dramático en nueve de los diez casos nuestros. El murmullo contínuo típico escuchado después de la ruptura se diferencia del que hay en ducto arterioso por la ubicación y calidad.

Los hallazgos del ECG y del roentgenograma y por la cateterización cardiaca son respasados. El diagnóstico definitivo puede hacerse por la angiocardiografía a por la aortografía retrógrada.

4. El cierre satisfactorio quirúrgico de un aneurisma del seno aórtico se ha relatado en ocho casos en los dos años pasados, utilizando la desviación cardiopulmonar con

un oxigenador de bomba y con le perfusión coronaria retrógrada. La ruptura del aneurisma no causa la muerte immediata (excepto en el caso extremadamente raro de ruptura dentro del saco pericárdico).

Habitualmente el enfermo puede mantenerse bajo tratamiento médico por varios años si es necesario.

Sin embargo contando ya con el oxigendro de bomba, la demostración de una fistula cardioaórtica debe considerarse como una indicación fuerte de su clausura mediante la técnica de corazón abierto.

RESUMÉ

1. Bien que les anévrysmes congénitaux des sinus aortiques de Valsalva sont d'apparition rare, 71 cas de cette altération ont été rapportés dans la littérature. 10 malades de l'Université des Hôpitaux du Minnesota avec preuve clinique ou autopsique de cette malformation sont également compris dans ce rapport.

2. Sur 78 cas au total, 59 avaient subi une rupture d'anévrysme avec création d'une fistule cardio-aortique. Le siège le plus commun de la terminaison était le ventricule droit (34 cas).

3. L'auteur décrit la symptomatologie de cette lésion. La lésion essentielle est un manque de continuité entre l'anneau fibreux de la valvule aortique et les transmissions élastiques aortiques. Dans au moins six cas, l'histoire clinique et les constatations autopsiques suggèrent une fistule cardioaortique congénitale. Plus communément, l'anévrysme sans rupture est relativement asymptomatique, le malade ne constatant qu'un souffle cardiaque ou qu'une dyspnée légère. En contradiction avec les impressions relevés dans la littérature, la rupture de l'anévrysme ne fut pas un écènement soudain et daramatique dans 9 de nos 10 cas. Le souffle typique continu entendu après rupture se différencie de celui d'une persistance du canal artériel par sa localisation et sa qualité. L'auteur passe en revue les constatations électrocardiographiques, la radiographie et le cathétérisme cardiaque. Le diagnostic définitif peut être fait par angiocardiographie ou aortographie rétrograde.

4. Huit observations de fermeture chirurgicale satisfaisante de la rupture d'un anévrysme du sinus aortique congénital ont été rapportées pour les deux dernières années. L'auteur a utilisé un court-circuit cardiopulmonaire avec oxygénateur à pompe et perfusion coronaire antérieure. La rupture d'un anévrysme ne provoque pas las mort immédiate (sauf dans l'exemple extrêmement rare de rupture dans le sac péricardique). Dans les cas habituels le malade peut être soumis à une thérapeutique médicale pour plusieurs années, s'il en est besoin. Cependant, lorsqu'on dispose d'un oxygénateur, la mise en évidence définitive de fistules cardio-aortiques doit être considérée comme une indication formelle d'opérer leur fermeture à "coeur ouvert."

ZUSAMMENFASSUNG

1. Obwohl angeborene Aneurysmen des Aorten-Sinus (Valsalva) seltene Vorkommnisse darstellen, finden sich in der Literatur 71 Fälle dieser Art. Es wurden noch 10 Kranke aus den Krankenanstalten der Universität von Minnesota mit klinischer oder autoptischer Evidenz dieser Mißbildung in diesen Bericht einbezogen.

2. Von den insgesamt 78 Fällen war es bei 59 zu einer Ruptur des Aneurysmas gekommen mit Ausbildung einer cardio-aortalen Fistel. Die häufigste Abgangsstelle war der rechte Ventrikel (34 Fälle).

3. Beschreibung der Symptomatologie dieser Veränderung. Der wesentliche Befund besteht im Fehlen einer Verbindung zwischen dem annulus fibrosus der Aortenklappe und der elastischen Media-Schicht der Aorta. In wenigstens 6 Fällen waren Krankheitsverlauf und Sektionsbefunde vereinbart mit einer bei der Geburt bestandenen cardio-aortalen Fistel. In den meisten Fällen bleibt das nicht rupturierte Aneurysma relativ symptomenlos, und der Kranke wird nur ein Herzgeräusch oder eine leichte Kurzatmigkeit gewahr werden. Im Gegensatz zu wiederholten Literaturangaben war die Ruptur des Aneurysmas nicht ein so dramatisches Ereignis bei 9 unserer 10 Fälle. Das typische kontinuierliche Herzgeräusch nach der Ruptur läßt sich durch seine LLokalisation und Qualität differenzieren von den des offenen ductus arteriosus. Die Ergebnisse des EKG, der Thoraxrö-aufnahme und der Herzkatheterisierung werden besprochen. Die Diagnose kann endgültig gestellt werden durch Angiocardiographie oder retrograde Aortographie.

4. Über einen erfolgreichen Verschluß eines rupturierten angeborenen Aorten-Sinus-Aneurysmas auf chirurgischem Wege wurden in 8 Fällen berichtet innerhalb der letzten 2 Jahre unter Heranzeihung eines cardio-pulmonalen Kurzschlusses mit einem Pumpen-Oxygenator und retrograder coronarer Durchspülung. Die Ruptur des Aneurysnas hat keinen unmittelbaren Tod zur Folge, (ausser in den extrem seltenen Fällen einer Ruptur in den Herzbeutel).

Für gewöhnlich kann der Patient, wenn es möglich ist, mehrere Jahre unter interner Behandlung stehen. Zeigt jedoch der zur Verfügung steht Pumpen-Oxygenator, an so, bedeutet der zweifelsfreie Nachweis einer cardio-aortalen Fistel eine absolute Indikation dafür, sie zu verschliessen unter Anwendung der Technik des "offenen Herzens."

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SUMMARY OF CURRENT THERAPY

Management of Coronary Insufficiency

Acute coronary insufficiency may be transient, extended or continuing, presenting as: (1) paroxysmal angina pectoris, (2) the prolonged intermediate coronary failure syndrome, (3) or persistent coronary occlusion without or with myocardial infarction, or (4) as complicating pulmonary edema, or cardiac asthma. The differentiation of these four conditions in the acute attack of pain is rewarding in that the treatment must be specific to be most successful.

The history is usually characteristic in classical paroxysmal angina pectoris and dramatic relief of pain often follows carotid sinus massage or the Valsalva maneuver if the patient can do it. The specific therapy is sublingual, nitroglycerine 1/200 to 1/100 gr. (0.3 to 0.6 mg) or Cardilate (erythrol tetranitrate) ¼ gr. (15 mg.). The drugs are perfectly safe if the blood pressure is normally sustained or elevated, and may be used to abort an attack or as prophylactics preceeding stressful circumstances. Peritrate and Isordil 10 to 20 mg tid are prescribed as vasodilators in coronary artery disease.

The occasional patient with frequently *recurring paroxysms of angina pectoris* and angina decubitus, approaching *status anginosis*, requires careful attention as he may have an impending coronary occlusion. Carotid sinus massage, slowing the heart and oxygen inhalation may bring relief. Hospitalization is in order, especially if the patient has been taking 10 to 20 nitroglycerine tablets during an attack and has literally kept himself in a nitroglycerine atmosphere and lowered the systemic blood pressure to near critical levels. The possibility of such adverse and rebound effects calls for discontinuation of nitrites. Anticoagulants, especially Heparin concentrate 200 mg. in 1 cc. s.c. twice daily seems to be preferable to other anticoagulants for it also clears the blood plasma and reduces the blood lipids which cause sludging of the blood and interference with fibrinolysin. The evil day of coronary occlusion may thus be postponed. I have used continuous intravenous drip of nicotinic acid 300 mg in 1000 cc 5 per cent glucose per day to the point of flushing for 5 to 7 days with successful interruption of status anginosis.

The therapeutic test with potent nitrites sublingually may be applied with safety in the paroxysmal transient and *intermediate persistent coronary pain syndrome* only if the blood pressure is *high*, and not if it is low or normal. Even in the patient with hypertension, however, nitroglycerine and erythrol tetranitrate rarely relieve the continued pain of the intermediate syndrome and narcotics must be resorted to. However, in the intermediate syndrome with *high* blood pressure the subendocardial ischemia is due to the high intracavitary pressure and therapy indicated is an antihypertensive regimen with Serpasil 2 mg. I. V. or Singoserp 4 mg. I. V. and/or oral, or Ismelin or guanethidine 12.5 to 25 mgm tid. Heparinization should be instituted and maintained.

In the intermediate pain syndrome with *low* blood pressure, sympathomimetic amines such as Aramine, Wyamine or Vasoxyl (15 mg. I. M. repeated prn), or Levophed 0.4 mcg/ml (I. V. by drip infusion) 4 mg in 1000 ml 5 per cent glucose are rationally exhibited with some success. The restoration of the systemic blood pressure to more effective levels improves the coronary flow through the intramural arteries down to the subendocardial tissues where ischemia is generally considered to be responsible for the cardiac atony and dilatation with persistent pain and the electrocardiographic changes of ST sagging and depression. Heparinization is certainly in order.

Acute coronary insufficiency of coronary occlusion is heralded by dramatic and serious symptoms and signs which call for emergency therapy. Excruciating pain usually dominates the clinical picture but cardiac asthma or pulmonary edema, extreme dyspnea and cyanosis may be equivalent or substituted symptoms. Narcotics, as morphine sulfate 15 mg. or Demerol 100 mg. or phenazocine 2 mg. I. M. or I. V. are sovereign remedies and are injected as soon as possible to relieve the pain, allay anxiety and may relax bronchospasm. Atropine sulfate 0.5 mg to 1.0 mg is usually added to block the gastrocardiac and the coronary reflexes.

The coronary occlusion or thrombosis pain may occasionally be accompanied by a transient elevation of the systemic blood pressure levels initially, which usually promptly begins to drop to low levels. Under such circumstances nitroglycerine or Cardilate may precipitate shock and syncope. Coronary occlusion by embolism or thrombosis is usually but not always followed by clinically apparent myocardial infarction with a leucocytosis, increased erythrocytic sedimentation rate, and increased S. G. O. Transaminase levels. Myocardial infarction may develop in rare instances without coronary occlusion.

Myocardial infarction with or without coronary occlusion calls for the most meticulous care. Oxygen is administered in 100 per cent concentration by mask under pressure of 4 cm of water especially if severe dyspnea, cyanosis or pulmonary edema have developed. The patient is placed in bed, in a semirecumbent position, and a plastic oxygen tent is setup and oxygen is supplied at the rate of 4 to 8 liters usually bubbled through 50 to 95 per cent ethyl alcohol to maintain a 40 to 60 per cent O2 atmosphere.

If acute left ventricular failure with pulmonary edema has developed, phlebotomy or the use of tourniquets placed around the extremities in the axilla and groins and each alternatively released for 5 minutes every 15 minutes, is resorted to.

The electrocardiogram is taken for confirmation and for the detection of any disorder of the cardiac mechanism. An antiarrhythmic drug as potassium chloride 1 Gm. quinidine 200 mg. or Pronestyl 250 mg. Atarax, or Mellaril 10 mg. is given p. o. or as otherwise indicated. If acute left ventricular failure is present and the heart's rhythm is regular, Cedilanid D 0.8 mg or Digoxin 0.75 mg is injected intravenously and half the dose repeated if indicated in one or two hours.

Any significant fall in systemic blood pressure is the indication for the use of sympathomimetic amines as Aramine 0.5 mg to 5 mg. I. V. or I. M. or by infusion of 25 to 100 mg. in 500 cc. of 5 per cent glucose; or Levophed 4 mgm in 1000 cc 5 per cent glucose solution as an I. V. infusion at a rate of 15 to 30 drops/min. as seems necessary to restore or maintain satisfactory blood pressure levels.

A sharp rise in systemic blood pressure, hypertensive crises, in the acute stage must be countered by antihypertensive drugs as Serpasil 2 mgm. I. M. or I. V. repeated until the blood pressure is gotten under control.

The patient's temperature, leucocyte count and erythrocyte sedimentation rate, and S. G. O. Transaminase determination should be made repeatedly, (as changes in these factors as fever, leucycytosis and the RBC sedimentation rate rise) may be delayed in appearance for 18 to 24 hours or not develop at all if the mass of necrotizing heart muscle is small.

The clotting time of the sludged blood may be increased by the high lipid cholesterol or triglyceride content of the patient's blood, which may also inhibit fibrinolysin. Heparin 100 mg. I. V. is then in order or Lipo-Heparin (Heparin concentrate) in 200 mg. doses may be continued twice daily through the critical period, or one of the dicumerol derivatives may be started with 300 mg. dicumerol initially, and then 75 to 100 mg. once daily to keep the prothrombin activity between 25 and 15 per cent of normal.

Constant observation and attention to every detail with frequent temperature, pulse, respiration, heart action, and blood pressure observation. Daily electrocardiographic recordings, leucocyte counts, erythrocytic sedimentation rates and S.G.O.T. (Transaminase) levels should be determined.

Aminophyllin 0.25 to 0.50 gm in 20 cc of isotonic saline may be given slowly intravenously or in a 5 per cent isotonic solution high in the rectum. The latter only occasionaly relieves the pain but relaxes bronchospasm and often seems to improve the pulmonary circulation. If pulmonary edema develops in spite of tourniquet trapping or phlebotomy and intravenous digitalization with Cedilanid D 1.8 to 2 mg, then a saluretic as Thiomerin 1 to 2 cc I. M. or Esidrix 25 to 50 mg a day p. o. may be effective. If the patient is not vomiting, oral dihydrochlorothiazide or Esidrix 50 to 100 mgm doses p. o. may be desirable for prompt effectiveness.

The patient should be placed in the most comfortable position sitting in bed or in chair until the attack of pain has been gotten under control and the hemodynamics, blood pressure and respiratory function are restored to normal.

After an attack it is desirable to keep the patient in bed under observation for several days to a week to determine the extent of organic changes in the heart and lungs. Serial electrocardiograms along with the temperature, pulse, respirations, leucocyte counts, red blood sedimentation rates, SGOT levels, clotting time, prothrombin activity, venous

pressure and arterial pressures must be observed to determine the status of the patient and how long he is to be kept in bed.

Heparinization, coronary vasodilators digitalization, diuresis, restrictions in salt intake and physical activities and rehabilitation depend upon the chemical clinical findings in each individual patient.

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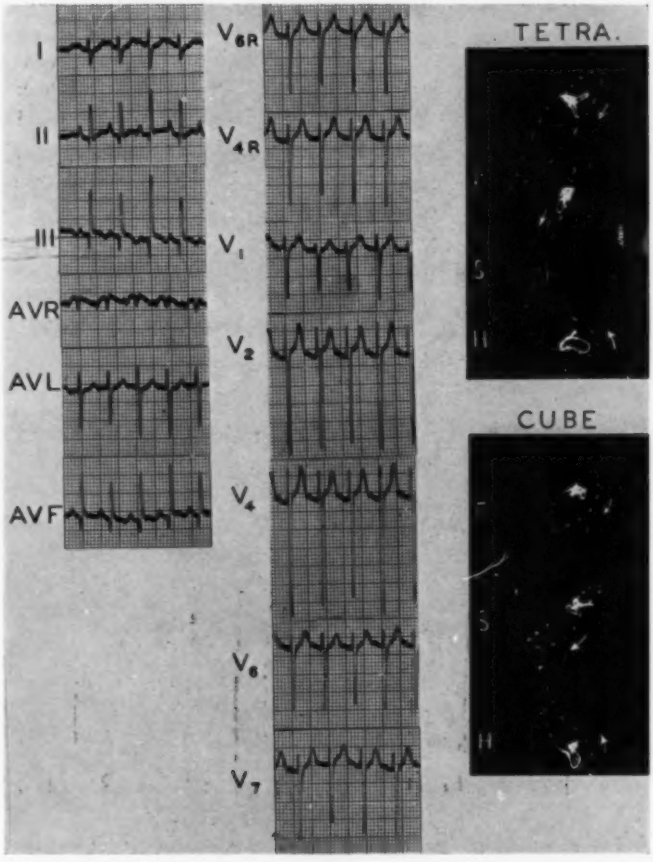
ELECTROCARDIOGRAM OF THE MONTH

Electrocardiogram and vectorcardiogram of an eight month old cyanotic infant with physical and roentgenographic findings typical of tetrology of Fallot. This diagnosis was varified by cardiac catheterization and cineangiocardiography.

Right axis deviation is present. All of the precordial leads show small R waves followed by deep S waves. Precordial leads recorded one interspace above and one interspace below the usual level were similar to those illustrated. The spatial QRS loop (recorded with both the tetrahedron and cube systems of vectorcardiography) is inscribed initially anteriorly, superiorly and to the left, but the greatest portion of the QRS loop is directed, posteriorly, inferiorly and to the right. The hozizontal projection of the QRS loop is inscribed in a counterclockwise manner in both systems.

Electrocardiograms revealing right axis deviation accompanied by small R waves and deep S waves in the commonly recorded precordial



leads are not infrequently seen in the presence of right ventricular hypertrophy. In some instances, precordial leads recorded over the right chest reveal large R waves, but as demonstrated, this is not universally true. Regardless of the absence of large R waves in the right precordial leads, such tracings are suggestive of right ventricular hypertrophy. Right axis deviation is also apparent in the vectorcardiogram, and the horizontal loop is inscribed in a counterclockwise manner, and posteriorly as well as to the right.

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The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

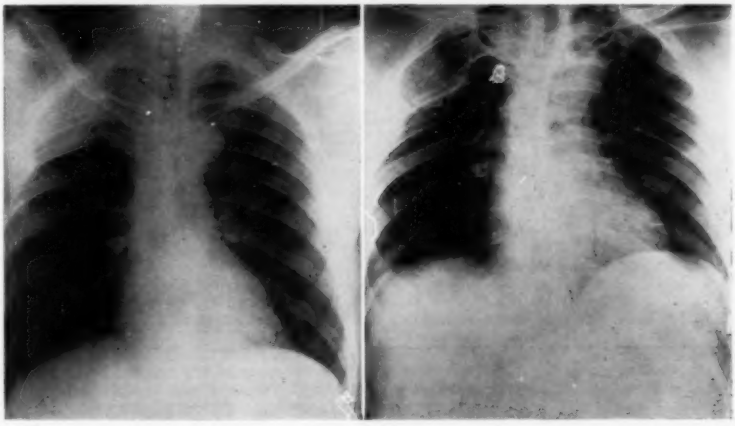
X-RAY FILM OF THE MONTH

A 58 year old negro came to the hospital complaining of right shoulder pain and some weakness of his right arm. He had noted the onset of this right back and shoulder pain approximately six months prior to admission. At that time he was given some pills which seemed to relieve the pain. He continued his work as a stevedore until one week prior to admission when he developed a new productive cough and an aching sensation in his right shoulder. On the day of admission the back pain increased in severity and he came to the hospital. There was no history of dyspnea, weight loss, or night sweats.

Physical examination was not significant, except for the right posterior thorax. There was noted along the border of the right scapula and extending to the vertebral column, a poorly defined area of tenderness and fullness. Breath sounds were present and there were no rales or dullness to percussion. Neurological examination revealed minimal weakness of the right arm. His hemogram and urinalysis were within normal limits. Routine x-ray film examination of the chest (a) showed a fairly large homogenous bilobulated density in the lateral apical portion of the right upper chest. The appearance was suggestive of an apical empyema; however, bucky films were requested since the possibility of a tumor involving the ribs could not be ruled out.

ANSWER

A bucky film (b) demonstrated an expanding bone lesion involving the proximal half of the fourth right rib. The bone lesion was cystic in nature and the diagnosis was fibrous dysplasia, or giant cell tumor. The lung fields were clear. A skeletal survey was negative and there was no sign of any endocrine abnormality. On December 15, 1958, he was explored and a 24 cm. portion of the posterior fourth rib and a 10 cm. portion of the fifth rib were excised with adherent intercostal muscles and pleura. Pathological examination revealed fibrous dysplasia of the bone. A second skeletal survey was completely negative.



A B

Diagnosis

Monostotic fibrous dysplasia of the fourth rib posteriorly.

Fibrous dysplasia of the bone is a disorder which involves as its primary feature the skeletal system. In some cases the skeletal aberration may constitute the entire disorder. In other cases, the skeletal disorder is associated with one or more non-elevated, light, yellow to tan, areas of cutaneous pigmentation. If endocrine abnormalities are present as well, the case is one of Albright's disease.

The dominant pathology of fibrous dysplasia is bone re-absorption, fibrosis of the marrow spaces, and substitution of poorly formed and unorderly arranged cancellous trabeculae for the original cancellous and cortical bone. If only one bone is effected, the term "monostotic" fibrous dysplasia may be applied. If several bones are involved and there are no associated endocrine abnormalities, the term "polyostotic" fibrous dysplasia may be used. Most cases of fibrous dysplasia are of the polyostotic variety, although monostotic lesions are fairly common. Solitary involvement of a rib has been reported many times in the past. There are no doubt numerous other cases of monostotic fibrous dysplasia which have been interpreted as bone cysts. The etiology of the disorder is unknown with no familial or hereditary tendencies.

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3 Zimmer, J. F.; Dahlin, D. C.: Pugh, D. G., and Clagett, O. T.: "Fibrous Dysplasia of Bone: An Analysis of 15 Cases of Surgically Verified Costal Fibrous Dysplasia," *J. Thoracic Surg.* 31:488, 1956.

ROBERT J. WILDER, M.D.
Baltimore, Maryland

The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with brief history. Please submit material to: Benjamin Felson, M.D., chairman, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

Treatment of Cardiac Arrhythmias with Hydroxyzine*

JAMES A. SALMONS, M.D., F.C.C.P.**
Santa Cruz, California

A report on the effectiveness and safety of hydroxyzine in treatment of various arrhythmias[1] suggested the drug for clinical trial in the four cases reported below.

In the previous evaluation of hydroxyzine, it was noted that the ideal anti-arrhythmic agent should be effective in arrhythmias of various types and etiologies, and possess a wide margin of safety. When acute abnormal rhythms require rapid treatment, such a drug should restore normal sinus rhythm quickly. The idea anti-arrhythmic agent should also be suitable for long-term prophylactic therapy.

Hydroxyzine (oral,† I. M., I.V.††) was reported to be clinically effective in treatment of acute arrhythmias, particularly those which disturbed ventricular rhythm. Beneficial effects occurred most frequently in patients with ventricular premature beats, paroxysmal tachycardias (auricular and ventricular), and in patients with ventricular extrasystoles complicating auricular fibrillation.[1] The drug was found to be safe, easily administered and nontoxic.[2-11] While the mechanism of action of hydroxyzine on cardiac rhythm is unknown to date, it appears that some direct myocardial effect may occur. It has been reported that in several patients treated with hydroxyzine, normal sinus rhythm resulted either during intravenous injection or within seconds thereafter.[1]

In addition, other properties of hydroxyzine contribute to its usefulness as an anti-arrhythmic agent. Since hydroxyzine is an effective, safe ataractic agent, its calming effect is of particular value in allaying the anxiety and apprehension of patients with cardiac arrhythmias, without impairing mental alertness. Hydroxyzine is not a cortical depressant and willn ot increase gastric secretion. The drug does not significantly lower blood pressure or produce quinidine-like side effects.

Case Reports

1. A general surgeon, age 35, reported a history of auricular and ventricular premature contractions which began in 1952. On the appearance of his first attack of ventricular pre-mature beats, he was advised to restrict use of coffee and tobacco. With these measures, he remained free of attacks until 1955. Over the following year, the condition became severe and required hospitalization in 1956. An exhaustive cardiovascular workup failed to reveal the etiology of the disorder. He was placed on a regimen including high doses of reserpine (0.5 mg., twice daily) and other sedation, and with complete abstinence from coffee and tobacco, he again did well until early in 1958 when the attacks of auricular and ventricular premature contractions resumed with increasing frequency, and would commonly lead to attacks of paroxysmal auricular fibrillation, accompanied by considerable gastrointestinal discomfort due to abdominal distention with gas. At his request, digitalization was withheld and he was placed on three to five tablets (9 to 15 gr.) of quinidine daily; reserpine was discontinued. He led a miserable existence on this regimen which apparently only aggravated his gastrointestinal symptoms. A GI series (exclusive of small bowel), barium enema, and gall bladder series did not demonstrate evidence of pathology. He was placed on antispasmodics (Cantil, piperidolate hydrochloride) in addition to

*Supplied by Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.
**Santa Cruz Medical Center.
†Vistaril Capsules (brand of hydroxyzine pamoate), Pfizer Laboratories, Div. of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.
††Vistaril Parenteral (brand of hydroxyzine hydrochloride), Pfizer Laboratories Div. of Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

quinidine; nevertheless, he was in a constant state of physical discomfort, in addition to his anxiety that an attack might occur while he was performing a surgical procedure.

In July of 1958, he was digitalized; 0.25 mg. of digoxin were required three times daily, alternating with a twice daily schedule. In addition, despite his discomfort, it was necessary for him to continue taking five to six quinidine tablets (15 to 18 gr.) daily. In October of 1958 the use of hydroxyzine was suggested and he was subsequently placed on Vistaril Capsules, 50 mg., three times daily, and 100 mg. at bedtime. Under this routine, he was able to discontinue the use of quinidine, and reduce the dosage of digoxin from 0.25 mg. three times daily to 0.25 mg. twice daily. Since instituting treatment with Vistaril, he has not had an attack of paroxysmal tachycardia and has been relieved of many of his previous anxieties. He does have occasional paroxysmal ventricular contractions, but has not had an 'attack' of paroxysmal tachycardia.

2. Mr. W. K., age 68, was seen in consultation two days after an exploratory gastric surgical procedure. Two years prior to admission for the present complaint, he had a massive anterior myocardial infarction. No maintenance cardiac therapy had been employed until the onset of his present illness. Two days after the exploratory procedure, he exhibited a rapid pulse rate with moderate hypotension, and was perspiring profusely. It was felt by his private physician that he had suffered another coronary attack, and measures to combat shock were immediately instituted. An emergency electrocardiogram revealed a supraventricular paroxysmal tachycardia, rather than an infarction. Carotid sinus pressure, pressure on the eyeballs, Vaisalva's maneuvers and other procedures provided no relief. He was then given 0.8 mg. of Lanatoside C intravenously. Serial tracings were taken at 10-minute intervals, as well as careful checks of blood pressure and pulse. After one hour, his condition had deteriorated, systolic blood pressure had dropped 40/0, he was perspiring profusely and the situation was desperate. He was then given 50 mg. of Vistaril intravenously over a three-minute period. In seven minutes he had promptly converted to a normal sinus rhythm of 80, his blood pressure returned to normal, and he required no more drugs throughout his hospital course.

3. Mr. D. C., age 74, had several attacks of supraventricular paroxysmal tachycardia without warning of onset. Since he became faint and fell during each attack, the possibility of injury was of considerable concern to him and the physician. He was first seen in consultation at the time of his next attack. Intravenous digitalis (0.8 mg. Lanatoside C) was admiinstered. He responded promptly, and subsequently was discharged from the hospital. Shortly thereafter he was digitalized (Gitalin 3.5 mg.) and placed on a heavy maintenance dose (0.5 mg. daily) in addition to receiving 12 to 15 gr. of quinidine sulphate daily. Several weeks later he was seen in acute distress with another attack of supraventricular paroxysmal tachycardia. A rather desperate situation had arisen since he could not receive further digitalis, and quinidine had caused him to be confined to bed because of severe bowel incontinence (diarrheal). He was given 50 mg. of Vistaril intravenously and reverted to a normal sinus rhythm within 10 minutes.

He is now taking 50 mg. of Vistaril (1 capsule) four times daily and has had no attack in the past 10 weeks. Other drugs have been discontinued.

4. Mrs. A. B., age 60, appeared in the office with supraventricular paroxysmal tachycardia, rate 186. No apparent organic heart disease was present. The usual maneuvers were tried without success. Angina pain was beginning to appear because of the marked myocardial ischemia resulting from decreased cardiac output. Intravenous Lanatoside C (0.8 mg.) was tried without success. She was then given 50 mg. of Vistaril intravenously and reverted to normal sinus rhythm (rate 68) in less than eight minutes.

Toxicity to Para-aminosalicylic Acid and Isoniazid

JOSEPH ADRIANY, M.D., F.C.C.P.*
Mount Vernon, Missouri

PRIMUM NON NOCERE: this advice of the ancients to physicians is still with us today. We have to remember it whenever we treat patients with drugs.

A case of toxicity developing after administration of para-aminosalicylic acid (PAS) and isoniazid (INH) is described.

This 62 year-old white woman who was admitted for treatment of pulmonary tuberculosis November 1, 1957, had Mycobacterium tuberculosis in her sputum and x-ray film showing extensive infiltration in the whole left lung field. A complete blood count done shortly before admission showed normal red blood count and hemoglobin, also normal white count and differential count. On admission, slight anemia was present with 11 grams of hemoglobin, white count and differential was within normal limits. Before admission, she was treated daily with streptomycin injections for a period of one month. She was started on para-aminosalicylic acid 15 grams daily and isonicotinic acid hydrazid 200 miligrams daily on November 5, 1957. Her fever soon subsided and in January, 1958 her temperature became normal. Her blood study in December, 1957 showed slight anemia and granulocytopenia of 30 per cent and lymphocytosis of 66 per cent of a total count of 6,800 white cells. In December, she complained of gastrointestinal upsets and on January 31 she developed an erythematous rash all over her body. Pruritus was also present. The rash subsided, but reappeared on February 13. PAS was then discontinued for a week and she was discharged to home treatment on a regimen of PAS and INH in the usual dosage to be continued indefinitely.

She continued to take these drugs at home, had gastrointestinal upsets and noticed a slowly increasing numbness in her lower limbs which became "stiff." Numbness appeared first in her toes, continued to feet, then appeared in her hands, these becoming increasingly clumsy. Due to this numbness and a lack of feeling in her feet, she became unable to walk in January, 1959. She was readmitted in February with symptoms of numbness and feeling of formication in all extremities and inability to walk even with help. Her blood study revealed slight anemia with 10 grams of hemoglobin granulocytopenia of 24 per cent, lymphocytosis of 76 per cent and 4,000 white blood cells. Peripheral blood smear showed anisocytosis, hypochromia, increase of lymphocytes with some prolymphocytic type of cells and an occasional lymphoblast, reduction in the number of platelets, and an occasional nucleated red blood cell. Morphologic appearance was suggestive of aleukemic lymphatic leukemia. Bone marrow biopsy showed no abnormality of maturation of the red blood cells and of the white cells, with a mild shift to the left, no increase of lymphocytes. There was no indication of leukemia. Another bone marrow biopsy done in April, 1959 showed only an overall decrease of cells of the erythroid series.

Blood study repeated at weekly intervals showed further increase in lymphocytes up to 81 per cent, granulocytopenia 15 per cent and a decrease of hemoglobin to 7.9 grams.

After a single blood transfusion her hemoglobin increased to 12.1 grams. However, lymphocytosis and granulocytopenia persisted. She was treated with pyridoxine, vitamin B complex and trinsicon and showed clinical improvement. The numbness gradually disappeared, feeling in hands and feet returned, so she is now able to walk again without help.

In contrast to the damage to the hematopoetic system, the following case report illustrates another aspect of PAS and INH toxicity.

W.B.: This 50 year-old white man was admitted March 9, 1954 with far advanced pulmonary tuberculosis. PAS, 12 grams daily, and INH, 300 miligrams daily, were started March 18, 1954 and continued regularly until April 19 when he developed fever. Until then, he was losing weight, having lost 12 pounds in two weks. However, x-ray films showed clearing of the infiltration. On April 24, 1954, he had high fever and a generalized rash appeared. All medication was stopped and his temperature returned to normal May 4, 1954, but jaundice appeared. Isoniazid was tried again and his temperature increased to 103°. He became irrational, highly jaundiced requiring sedation and restraint. Later he ceased to respond, was moaning loudly, became more jaundiced on May 8, 1954 and expired in hepatic coma May 9, 1954. Autopsy showed deep icterus, deeply bile stained free fluid in the abdomen. The lungs

*Missouri State Sanatorium.

showed tuberculosis and hemorrhagic infarction. Extensive degeneration necrosis was found in the liver parenchyma, with cords of regenerating tissue and proliferation of bile ducts. Occasionally there were seen solitary multinucleated giant cell formations which appeared to be fused regenerating epithelial tissue. The histological features were of acute yellow atrophy. Dr. D. Gorelick, pathologist, reported: "Findings reveal an acute yellow atrophy of the liver which, in view of the patient's history, was probably a toxic manifestation secondary to a reaction to para-aminosalicylic acid or isonicotinic acid hydrazide."

The following case of a fatal liver necrosis after treatment with PAS and INH is of a patient who underwent pneumonectomy for pulmonary tuberculosis successfully.

This 61 year-old white woman was admitted in January, 1956. Her sputum contained acid-fast bacilli and her x-ray films revealed evidence of extensive tuberculosis in the left lung. PAS and INH were begun in January and left pleuropneumonectomy was performed in March, 1956. She was discharged in July, 1956 to continue PAS and INH at home. Symptoms of indigestion, swelling of abdomen, bulky stools, fatigue and malaise developed and she was readmitted in January, 1957. No active tuberculosis was found and PAS was discontinued. Jaundice appeared in March, 1957, when liver function tests showed bromsufalein retention of 61 per cent. There was slight increase in serum alkaline phosphatase to 10 Bodansky units. The findings were typical of hepatocellular jaundice. The jaundice increased gradually and she died in hepatic coma in April, 1957.

Autopsy by Dr. Fred Coller revealed acute yellow atrophy of the liver on macroscopic and microscopic examination. Since the incubation period exceeded 10 months, viral hepatitis due to homologous serum hepatitis was considered unlikely.

Comment

Symptoms of severe toxic reactions to PAS and INH appear only in a minority of patients and therefore are thought to be due to sensitization, possibly to a protein drug combination acting as antigen, the toxin then possibly developing from a combination of the antibody with the antigen acting on the liver interfering with the metabolism of the liver cells probably by injury to the enzymes.

Investigation using PAS or INH combinations with proteins as antigens to produce allergy might possibly shed some light on this mystery.

Chest Percussion—A Simple and Efficient Teaching Method

MYRON NOTKIN, M.D., F.C.C.P.*
Montreal, Quebec

The purpose of chest percussion is, in the main, to outline the cardiac borders and width of the aorta and to determine where and to what extent the air content of the lung has been altered from the normal. Well defined resonance or dullness is simple for the student to differentiate but the various grades between the extremes provide some difficulty and uncertainty. Resonance is a relative term and may be differently conceived by different individuals unless a universally accepted standard is used as a basis of reference. Few students seem to appreciate the facts (1) That it is not so much amplitude as frequency — not so much loudness, as pitch — that makes a sound comparatively dull, and (2) That each successively higher note in the musical scale is duller than the note immediately below. The musical scale, in consequence, should be the standard used in attempts to determine relative resonance or dullness. The whole normal chest, apart from the cardiac area, is resonant but there is a difference of at least an octave between the note at the base and the note at the apex. It therefore follows that the difference between any two notes is best determined by setting them mentally in their respective positions in the musical scale. If the second percussion note has to be mentally sung higher in the scale than the first, it is clearly the duller of the two. If the second note appears to be lower in the scale or the result is doubtful, the comparison should be reversed for the ear can perceive the change from resonance to relative dullness much more acutely than the reverse. This upscale sequence must be constantly sought to obtain a sharp, clear-cut and often striking distinction.

The lung itself being roughly cone-shaped, may be conceived as a compound musical percussion instrument consisting of a series of thin-walled drums, each of the same height (empirically two inches) but decreasing in circumference gradually from the base upward. If each were percussed individually and successively from the base, the notes obtained would be expected to rise somewhat like the rise of the musical scale. Indeed, such a rise actually occurs in every normal chest when percussed in this manner. On the basis of accoustics and the accepted principles of perception of sound by the auditory apparatus it is obligatory to carry percussion from base to apex in order to avoid handicapping the auditory system upon which, almost entirely, this procedure depends. To those unaccustomed to its use, this method is best demonstrated posteriorly where heart dullness and breast tissues do not interfere with the examination.

In percussing the back of the chest the patient should sit slightly bent forward with arms hanging between the knees to bring the scapulae as far laterally as possible. The lower limit of lung resonance should

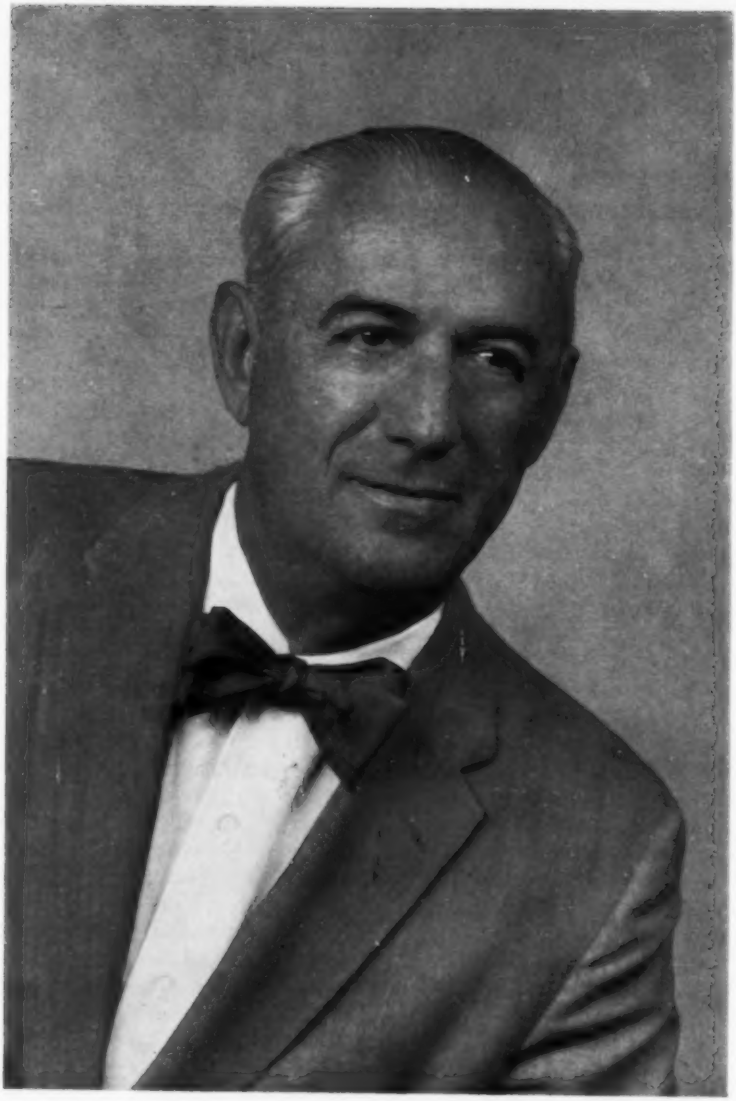
*From the Department of Medicine, McGill University, the Royal Edward Laurentian Hospital and the Department of Medicine, Montreal General Hospital.

be established by percussing from a hand's breadth above the 10th rib downward (from resonance to dullness) and marked with skin pencil. The extent of diaphragm excursion should then be determined and marked. To detect any superficial abnormality at the lung base, an extremely fine percussion tap is made just below the line of resonance. This will necessarily produce a dull or flat note to be used for comparison in the next step. The same fine percussion is repeated immediately above this line. If this note is slightly resonant in contrast to the previous one, no effusion or pleural thickening can be present, but if this note is as dull as the previous one, percussion should be continued upward with the same fine tap. Should the successive notes become gradually more and more resonant, the presence of pleural effusion or thickened pleura is indicated, being heaviest at the base and diminishing gradually upward. Differentiation between the two is made in the usual way including test for shifting dullness and contralateral Grocco triangle which must be looked for with extremely light percussion. Percussion of the rest of the chest should begin two or three inches above the lower limit of the lung in order to avoid the thin wedge of lung at the base which, in fact, has already been percussed. The percussion line should run upward half-way between the scapula and the spine. A series of moderately firm, one-stroke percussion taps is then fairly rapidly carried upward at about two-inch intervals to the upper border of the trapezius. If the examiner sings mentally each note as it is produced during percussion of a normal chest, a series of notes will result rising in pitch smoothly as in the musical scale. This may be called THE NORMAL MUSICAL GRADIENT OF THE LUNG. As such it precludes the probability of any change in the relative air content in the successive sections of the lung. Any skipping of several notes in the scale indicates pathological replacement of air in the area where this occurs. This may be followed by a series of identical notes or a further skipping to indicate that the pathological process continues upward as far as this occurs. On the other hand, any sudden reversal to a lower note in the scale indicates an increase of air content beyond the normal in that area. Such changes become evident even when the abnormality is minimal. The extreme apex is percussed in the usual way and the width of the shoulder strap determined. When the right and the left sides of the lung have been individually percussed in this manner and the gradient of each determined, it is then, and only then, logically permissible to compare one with the other, for there are now available for comparison two known factors, namely two normals, two abnormals or one normal and one abnormal, and the pitfalls of comparing two unknowns are avoided.

During the examination of the front of the chest the patient should sit with spine erect. Examination of the base should follow the procedure already outlined in discussing percussion of the base posteriorly. The cardiac borders should then be percussed. If gastric tympany interferes with the complete outline of the left border percussion of the apical portion should be made during deep inspiration to the point of dullness. In the average individual at rest the apex will lie 1 cm to the left of this point. Each lung is then percussed upward beyond the midclavicular area to the apex, avoiding cardiac borders. Because of the de-

creasing subcutaneous tissues at the upper third, the percussion tap should become much lighter there. When heavy breast tissue is present it may be necessary to run the percussion line from the anterior axillary line at the base diagonally up to the clavicle. This route actually produces a better scale sequence, but then the lower part of the lung medial to this line has to be percussed independently with a firm stroke.

Percussion is an active inquiry and must be altered (fine, light, moderate or firm) depending on the questions to be answered and the nature of the chest to which these questions are addressed. A large amount of pleural effusion in an emphysematous chest and a small amount in the chest of a child may both be missed unless fine percussion is used. Fine percussion must be used to detect a Grocco triangle particuularly when the amount of effusion on the contralateral side is small. The more firm the percussion the more deeply penetrating and more divergent are the vibrations and therefore the greater the volume of lung which responds. Such percussion cannot be used for localizing a lesion.



DR. M. JAY FLIPSE

M. JAY FLIPSE TAKES OFFICE AS COLLEGE PRESIDENT

Dr. Flipse was born in northern New Jersey, just outside New York City, the second son of the second son of a Dutch immigrant. His father was a minister of the Dutch Reformed Church, a protestant denomination.

He was educated in the public schools of Passaic, New Jersey, and later when the family moved to Chicago, he graduated from high school in that city.

His mother's father had been a pioneer in another Dutch settlement which founded the town of Holland, Michigan, and established there a college called Hope. It was from this school that Dr. Flipse graduated in 1917 with the degree of A.B. and then went to the medical school of the University of Cincinnati. Here he graduated with highest honors in his class in 1921 with the coveted M.D. degree.

The next two years were spent in graduate study at the Cincinnati General Hospital, after which he started practice in the field of medicine in the young booming town of Miami, Florida.

The next six years were exciting years with the boom and bust of Miami, the severe and devastating hurricane of 1926, the citrus fruit fly of the late twenties and finally the great depression of '29. In this same year, M. Jay had an opportunity to study with Paul White in a short course in cardiology.

By this time the young doctor had identified himself with a number of medical organizations including the State Tuberculosis Association and the Jackson Memorial Hospital, now the teaching facility of the Medical School of the University of Miami. In the work of tuberculosis, he was successful in seeing Florida's first unit for treatment of pulmonary tuberculosis built at the Jackson Memorial Hospital. He was also on the committee which helped to lay the cornerstone for the first State Tuberculosis Sanitorium at Orlando, Florida.

Sometime in 1935 or 1936, he met the dynamic Murray Kornfeld and became a member of the American College of Chest Physicians. He has served this organization in many capacities for more than 20 years, first as Governor, then as Regent, then as Vice President, President-Elect, and now President.

He is also a Fellow of the American College of Physicians, Fellow of the American Medical Association and Past-Chairman of the Section on Chest Diseases in the American Medical Association, and a member or Fellow of some twenty other specialty organizations. He has been in private practice in Internal Medicine since 1923 and is identified with the Miami University School of Medicine in the capacity of Clinical Assistant Professor of Medicine and Chief Consultant in the Service of Pulmonary Diseases at the Jackson Memorial Hospital.

Dr. Flipse and his wife, Alice, have two sons, one of whom, Thomas E., is a physician who is married to a physician. Dr. Thomas E. Flipse has already expressed his interest in the College and his application for Associate Fellowship is pending. Dr. M. Eugene Flipse, Professor of Diseases of the Chest and Public Health at the University of Miami School of Medicine, is a nephew of the President.

BURGESS L. GORDON JOINS AMA

Dr. Burgess L. Gordon, past-president of the College, has accepted a position as Associate Editor of the *Journal of the American Medical Association*. On July 1, 1960, he will move to Chicago to assume his duties with the American Medical Association. Before coming to Chicago, Dr. Gordon served as Director of Medical Education and Research of the Lovelace Foundation, Albuquerque, New Mexico. Dr. Gordon has had a long and distinguished career in medicine. He served as Clinical Professor of Medicine at Jefferson Medical College, the school from which he graduated in 1919, as Director and Physician-in-Chief of Barton Memorial and White Haven Divisions of Jefferson Hospital and as President and William J. Mullen Professor of Medicine of Woman's Medical College of Pennsylvania. He retired from military service with the rank of Colonel after serving as commanding officer of various United States Army stations in the Near and Far East. During the years 1947-51, he served as consultant to the Surgeon General of the Army. He has published more than 200 articles in medical journals and textbooks and was chairman of the editorial committee for the book, *Clinical Cardiopulmonary Physiology*, sponsored by the American College of Chest Physicians. This book is presently being completely revised and a new edition under the co-chairmanship of Dr. Gordon and Dr. Ross C. Kory is presently in press.

JOINT MEETING WITH AMA IN 1961

By action of the Board of Trustees of the American Medical Association and the Board of Regents of the American College of Chest Physicians, a joint scientific program will be developed by the Committee on Scientific Program of the American College of Chest Physicians and the Section on Diseases of the Chest of the American Medical Association.

This program, to be presented at the 1961 annual meeting of the American Medical Association in New York City, will be the first joint meeting in the history of the two societies.

The College will shorten its annual meeting by one day, with its scientific sessions opening on the Saturday preceding the meeting of the American Medical Association instead of Friday as has been the custom during the past quarter of a century. The joint sessions with the Section on Diseases of the Chest of the American Medical Association will be held on Monday following the College meeting.

As a result of this arrangement, more members of the American College of Chest Physicians will be able to stay over for the scientific sessions of the Section on Diseases of the Chest and visit the splendid scientific exhibits of the American Medical Association.

The popular Fireside Conferences will be held on Monday night during the AMA meeting instead of Friday night as at past meetings. This will also be a joint session sponsored by both the American Medical Association and the College. The equally popular Round Table Luncheon meetings will be extended to Monday.

It is not too early to make your plans now to attend this meeting.

NEW CHAPTER OFFICERS

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MEDICAL SERVICE BUREAU

POSITION WANTED

Woman physician, ten years' experience in chest diseases, desires to re-locate. Seeking position in chest disease division of general or geriatric hospital in New York City area. Please address inquiries to Box 310B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Assistant to medical director wanted for 280-bed county, accredited hospital. Requirements: experience in chest diseases, internal medicine (geriatrics); New Jersey state license. Modern furnished accommodation and full maintenance at nominal cost; excellent pension plan combined with Social Security; free hospitalization, paid vacation, sick leave and holidays. Salary depends on experience and qualifications. Contact: Eugene Nargiello, M.D., Superintendent and Medical Director, John E. Runnells Hospital for Chest Diseases, Berkeley Heights, New Jersey.

Senior physician wanted for 280-bed county, accredited hospital. Requirements: approved internship and training chest diseases, experience in internal medicine (geriatrics), eligible for license in New Jersey or licensed in any state. Modern furnished accommodations and full maintenance at nominal cost; excellent pension plan combined with Social Security; free hospitalization, paid vacation, sick leave and holidays. Salary depends on training and experience. Contact: Eugene Nargiello, M.D., Superintendent and Medical Director, John E. Runnells Hospital for Chest Diseases, Berkeley Heights, New Jersey.

Qualified tuberculosis and chest physician wanted. Licensure and citizenship required. Duties: ward physician, general medical, assistant in surgery. Possible appointment Assistant Medical Director and Assistant Superintendent, depending on qualifications. Salary also depends on qualifications. Hospital fully accredited by Joint Commission. Medical and surgical tuberculosis programs, community 50,000. Civil Service, state retirement-Social Security plan. Excellent starting salary; $85 monthly deduction beautiful furnished home, all utilities and laundry. Please address replies to: R. E. Joseph, M.D., Superintendent, Oregon State Tuberculosis Hospital, Salem, Oregon.

ANNOUNCEMENT

The Colorado Chapter of the College, together with the Colorado Heart Study Club, Fitzsimons Army Hospital, National Jewish Hospital and University of Colorado School of Medicine, will sponsor a Postgraduate Course on Cardiopulmonary Disease at the Rehabilitation Center of the National Jewish Hospital in Denver on August 15 and at Fitzsimons Army Hospital, Bushnell Auditorium on August 20. The tuition fee is $10 per person. The program is as follows:

August 15

8:30 a. m. Registration

9:00 a. m. "Indications for Thoracotomy in Pulmonary Disease"
John R. Durrance, Moderator
Morgan Berthrong, Pathologist
John Campbell, Radiologist
George H. A. Clowes, Jr., Surgeon
Sidney Dressler, Internist

12:00 noon Business meeting, Colorado Chapter

12:30 p. m. Luncheon

2:00 p. m. "Physiology of Congestive Failure"
Giles Filley, Moderator
Chandler Brooks, Physiologist
George H. A. Clowes, Surgeon
Joseph Holmes, Internist
Abe Ravin, Cardiologist

August 20

9:00 a. m. Clinical Session with Case Presentations
Colonel Charles Christianson, MC, Moderator